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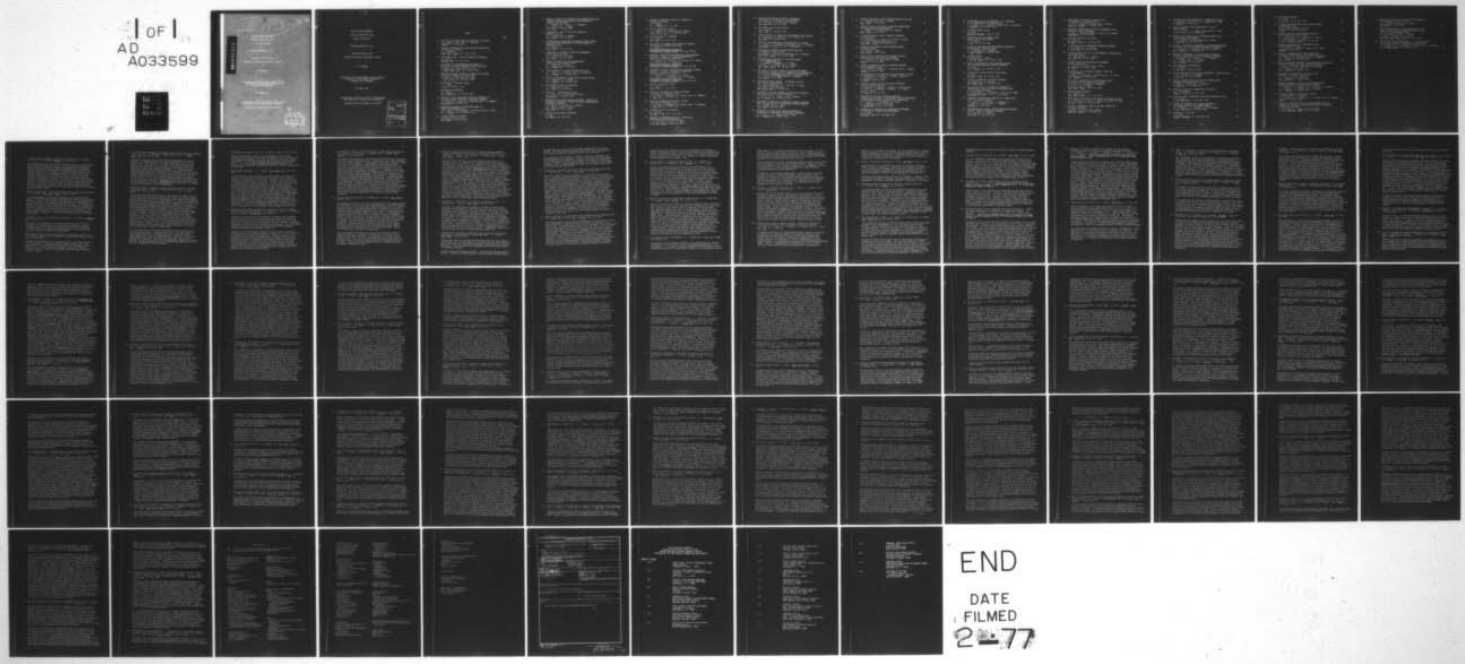

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TECHNICAL REPORT NO. 110

Abstract Reference List

Reviews of Pertinent Literature in Shock

L. B. Hinshaw

University of Oklahoma Health Sciences Center
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Oklahoma City, Oklahoma

18 October 1976

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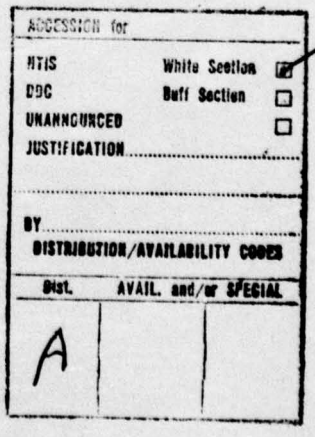

INDEX

1. The effect of severe trauma on urine loss of insulin. M. M. Meguid, F. Aun, and J. S. Soeldner. Surgery 79: 177-181, 1976.

   Six trauma patients and five healthy volunteers were given an intravenous glucose infusion (5 gm/hr) for 6 hrs. The serum insulin response and urine insulin excretion were measured and compared in the two groups. Glucose intolerance and serum insulin levels which were elevated but inappropriately low for the degree of glycemia characterized the trauma patients. Urine insulin concentrations and total urine insulin were increased significantly in the trauma patients. Renal function was similar in both groups, as determined by serum creatinine, blood urea nitrogen, and creatinine clearance. The increase in urine insulin concentration in the trauma patients reflected the higher serum insulin concentrations. A negative correlation was found between "insulin clearance" and serum insulin in both groups, indicating altered renal handling of insulin following injury which may be a contributory factor to the relative hypoinsulinemia of trauma.

2. Effects of transfusion on surviving and nonsurviving postoperative patients. W. C. Shoemaker. Surg. Gynec. Obstet. 142:33-40, 1976.

   In the pretransfusion control period, generally, the cardiorespiratory values of the nonsurviving patients were worse than those of the surviving patients. Moreover, the responses of nonsurvivors to a standardized test of therapy generally were less than those of survivors. The increase in oxygen availability to the tissues after blood transfusion in nonsurvivors was almost as great as that of survivors, but the increase in oxygen consumed by nonsurvivors was only about one-half that of survivors. This is of particular importance in the critically ill patient, as reduction in oxygen transport represents a major physiopathologic problem in postoperative deaths.

3. Cardiogenic shock: Can the prognosis be improved? R. W. Evans. Postgrad. Med. 58:79-85, 1975.

   The prognosis in cardiogenic shock remains poor despite improvements in treating other complications of acute myocardial infarction. In some situations, left ventricular function can be improved by increasing the vascular volume, but the benefits of increasing the cardiac output must be balanced against the risk of pulmonary edema.

   Monitoring of volume therapy is best done via the pulmonary route. The goal of drug therapy is to raise arterial blood pressure and make the heart pump more effectively.

   An aggressive approach will not cure great numbers of individuals because the basic problem of extensive myocardial damage remains, but it will identify those who are hypovolemic or who have other correctable contributory factors. Most important, this approach may help to identify therapies currently in use that may actually increase rather than lessen myocardial damage.

4. The effects of endotoxemia and bacteremia on gastrointestinal drug absorption in mice and rats. A. Hurwitz, D. Furtado, and R. R. Low. J. Pharm. Exptl. Ther. 192: 236-241, 1975.

   Endotoxin [lipopolysaccharide (LPS)] from four gram-negative bacteria injected i.v. delayed absorption of drugs administered in solution by gastric tube to mice and rats. Salicylate and quinine absorption was delayed at LPS doses from 50 to 400 μg/kg. Salicylate absorption was delayed by LPS when drug was given by gastric tube, while LPS did not affect drug levels when salicylate was given i.p. or intraduodenally. Bethanechol prevented the LPS effect and LPS pretreatment also protected against delayed absorption. LPS-treated rats retained more drugs in their stomachs after 30 min and their plasma salicylate levels were lowered. Everted intestinal sacs from LPS-treated rats transferred salicylate as well as controls. Thus, LPS delays gastrointestinal drug absorption solely by retarding gastric emptying. Escherichia coli urinary tract infection did not reproduce LPS delay of drug absorption, but the effects of systemic bacteria were similar to those of endotoxemia.

5. Somatostatin-induced changes in insulin and glucagon secretion in normal and diabetic dogs. H. Sakurai, R. Dobbs, and R. H. Unger. J. Clin. Invest. 54:1395-1402, 1974.

   In conscious dogs intravenously infused somatostatin (3.3 μg/min for 1 hr) caused prompt and sustained declines in mean plasma insulin and glucagon, even during alanine infusion and intraduodenal casein hydrolysate feeding; plasma glucose declined, but not significantly. 6.7 μg/min of somatostatin significantly lowered pancreatoduodenal vein glucagon and insulin within 2.5 min and profoundly suppressed their secretion throughout the infusion. Consistent bihormonal suppression occured at rates as low as 24 ng/kg/min, but was variable at 12 and 2.4 ng/kg/min. When somatostatin-induced (3.3 μg/min) hypoglucagonemia was corrected by exogenous glucagon, hyperglycemia occurred. In dogs with long-standing insulin-requiring alloxan diabetes 3.3 μg/min of somatostatin suppressed glucagon to 55 pg/ml throughout the 30-min infusion and lowered glucose by 36.4±6.1 mg/dl, about 1 mg/dl/min. Glucagon suppression was maintained despite alanine infusion, and glucose, which rose 20 mg/dl during alanine infusion without somatostatin, declined 58 mg/dl in the somatostatin-treated diabetic dogs despite alanine. Continuous infusion of somatostatin for 24 hr in five insulin-requiring alloxan-diabetic dogs suppressed glucagon and lowered glucose significantly, usually to below normal.

   It is concluded that in normal dogs pharmacologic doses of somatostatin virtually abolish insulin and glucagon secretion in the basal state and during hyperaminoacidemia. Hyperglycemia occurs during somatostatin-induced insulin lack only if hypoglucagonemia is corrected. Somatostatin suppresses glucagon in diabetic dogs and lowers their plasma glucose approximately 1 mg/dl/min, even when the gluconeogenic substrate alanine is abundant. Glucagon suppression can be maintained for several hours in such dogs and hyperglycemia is thereby reduced.

6. Hypoglycemia in neonatal sepsis. C. Y. Yeung. J. Ped. 77: 812-817, 1970.

   Twenty infected newborn infants who had hypoglycemia are presented. Seventeen had obvious clinical evidence of infection; 8 of them presented with hypoglycemic symptoms, which were controlled by raising the blood sugar levels. The infecting organisms were predominantly gram-negative bacilli. In 39 other infected infants who were normoglycemic, the bacteriologic findings were significantly different. Possible explanations are discussed.

7. Gram-negative bacteremia. W. R. McCabe. Adv. Intern. Med. 19:135-138, 1974.

   The increasing clinical familiarity with gram-negative bacteremia often causes us to forget that such infections have become a major medical problem only during the past 20-25 years. Prior to 1909, Jacob was able to collect only 39 instances of coliform bacteremia, including 13 of his own, from the world's medical literature. By 1924, Felty and Keefer had added 28 more cases from the records of the Johns Hopkins Hospital. Bacteremia caused by gram-negative bacilli other than Salmonella was still considered a rare clinical entity, however, until Waisbren's report of 29 cases observed during a relatively short period at Minneapolis in 1951. This report was the first to herald the appearance of gram-negative bacilli as the major cause of hospital-acquired infections. Since that time, the number of cases and deaths from gram-negative bacteremia has increased progressively each year. McCabe and Jackson demonstrated an eight-fold increase in the frequency of gram-negative bacteremia between 1951 and 1958. Subsequent, unpublished observations indicate that the incidence of this disease has increased almost 20-fold over the past 20 years. This article is a broad review of the etiology of septic shock.

8. Analysis of left ventricular function in response to afterload changes in patients with mitral stenosis. J. L. Bolen, M. G. Lopes, D. C. Harrison, and E. L. Alderman. Circulation 52:894-900, 1975.

   In order to assess left ventricular function in patients with rheumatic mitral stenosis, left ventricular function curves (plotting stroke work index vs left ventricular end diastolic pressure) were constructed using angiotensin to augment, and nitroprusside to reduce, afterload. Hemodynamic responses of these alterations in afterload were measured. Resting ejection fractions and qualitative assessment of left ventricular angiographic contraction abnormalities were also determined.

   Changes in left ventricular end diastolic pressure following afterload interventions could be linearly related to changes in mean aortic pressure, but mitral valve gradients were unaffected. Afterload reduction with nitroprusside did not augment cardiac output. Afterload elevation with angiotensin significantly depressed both cardiac output and calculated mitral valve areas. Patients with normal resting ejection fractions evidenced normal ventricular function curves and those with depressed ejection fractions showed flat or declining function curves. Contraction abnormalities, generally in the posterobasal area, correlated well with abnormal left ventricular function curves.

9. Microvascular control in intestinal mucosa of normal and hemorrhaged rats. H. L. Bohlen, P. M. Hutchins, C. E. Rapela, and H. D. Green. Am. J. Physiol. 229:1159-1164, 1975.

The mucosal microcirculation in innervated and denervated small intestine was studied using anesthetized rats. Denervation did not cause significant ($p>0.05$) diameter changes in the precapillary vasculature; however, venules did constrict significantly. These results indicate minimum neural control in the precapillary vasculature during the resting state. The innervated precapillary vasculature constricted during both the carotid occlusion reflex and hemorrhagic hypotension. The diameter of the denervated precapillary vasculature was unchanged during the carotid occlusion reflex and dilated during hemorrhage. The responses of innervated and denervated precapillary vasculatures were attributed to increased neural activity and autoregulatory mechanisms, respectively. Neither innervated nor denervated venules responded during the carotid occlusion reflex. During hemorrhage, however, innervated venules constricted and denervated vessels dilated. The vasoconstriction of the innervated vasculature during hemorrhage contributed to a stoppage of blood and epithelial detachment; these responses did not occur in the dilated, denervated vasculature. Therefore, neural vasoconstriction, qualitatively similar to that in normal animals during the baroreceptor reflex, is a contributing cause to the vascular and tissue impairment in the intestinal mucosa during hemorrhage.

10. Cellular metabolism in shock. W. Schumer and P. R. Erve. Circ. Shock 2: 109-127, 1975.

The changes that occur in the cells of peripheral and vital organs secondary to shock appear to be mainly in the energy pathways. The energy pathways are inhibited by the lack of oxygen; anoxia and energy deficit inhibit the membrane function. The membrane dysfunction interferes with the active transport of gluconeogenic substrate, such as glucose and amino and fatty acids, and allows potassium efflux and sodium influx. Gluconeogenesis is inhibited either by a direct effect of endotoxin on the gluconeogenic enzymes or by the lack of ATP. Further anoxia interferes with the oxidation of pyruvate and increases the intracellular and extracellular levels of lactate. The intracellular acidosis or the direct effect of endotoxin on membranes causes lysis or permeability of cellular and lysosomal membranes. Lysosomal hydrolases have been implicated in the cellular pathology of shock, the production of a myocardial depressant factor, and the effects on endothelial cells of the vascular system. Further ATP deficiency may alter protein biosynthesis.

Thus, the anaerobic metabolism that results from inadequate perfusion causes ATP deficiency, intracellular accumulation of lactate, and an increased serum level of lactate. The catabolism of fats and proteins produces acidic fatty acids, acetone bodies, and acidic amino acids in the serum, which the cell cannot absorb because its membrane function is disrupted. These metabolites compound the lactic acidemia and produce the metabolic acidemia of shock.

11. Effects of whole blood transfusion on forelimb weight and segmental vascular resistances in dogs previously injected with endotoxin. W. J. Weidner, R. L. Kline, E. F. Gersabeck, F. J. Haddy, and G. J. Grega. Circ. Shock 2: 165-174, 1975.

The aim of this study was to determine whether transfusion leads to excessive net fluid filtration and a disproportionate rise in extravascular fluid volume (EFV) in the forelimbs of dogs injected previously with endotoxin. Mongrel dogs were anesthetized with sodium pentobarbital and injected with either purified Escherichia coli endotoxin (5 mg/kg, iv) or saline, and after 2 hrs were transfused with 1000 ml of cross-matched whole blood over a period of 25 min. There was no change in the forelimb parameters in the saline-treated dogs before transfusion. After transfusion, forelimb weight increased markedly relative to control (22 g in 2 hrs). The weight gain was associated with increases in right atrial, aortic, and small vein pressures and hematocrit, but no change in segmental vascular resistances (SVR). Hence, this weight gain may be largely attributed to a rise in EFV subsequent to a rise in capillary hydrostatic pressure (P_c). In the endotoxin dogs, forelimb weight, pressures, and blood flows decreased and SVR increased as reported previously. After transfusion forelimb weight increased but failed to return to pre-endotoxin levels. This initial transient weight gain appeared to be largely due to an increase in vascular volume subsequent to a fall in SVR. These data provide no evidence for a greater rise in EFV after transfusion in endotoxin dogs than in saline-treated dogs. Additionally, these data also fail to support the fluid filtration hypothesis of circulatory shock.

12. Indomethacin: Lack of effect on lethality of endotoxin in rats. M. J. Reichgott and K. Engelman. Circ. Shock 2: 215-219, 1975.

The effect of indomethacin on lethality of endotoxin in lead-acetate-sensitized rats was studied. Rats (334±4 g, n=26) received intravenous injections of endotoxin in lead-acetate (5 mg/ml) 0.9% saline. The LD_{50} of endotoxin was 0.075 mg/kg. Lead-acetate caused no mortality at 24 hrs. Similar doses of endotoxin in lead-acetate were injected intravenously and 12% ethanol (0.6 M phosphate buffer, pH 8.0) administered by gavage to 39 animals. The LD_{50} was 0.064 mg/kg (not significant). An additional 40 animals received indomethacin (10 mg/kg) in alcohol buffer immediately before injection of endotoxin lead-acetate. The LD_{50} was 0.051 mg/kg (not significant). Indomethacin alone (10 animals) caused no mortality. The dose of indomethacin was sufficient to inhibit prostaglandin synthesis effectively for the 24-hr observation period. Indomethacin does not alter endotoxin-caused mortality in lead-acetate-sensitized rats.

13. Ultrastructural comparison of myocardial zonal lesions and myofibrillar degeneration in cats subjected to hemorrhagic shock. N. B. Ratliff. Circ. Shock 2: 221-231, 1975.

Healthy adult cats were subjected to hemorrhagic shock and were compared with control cats. At the completion of the shock period, right ventricular papillary muscles were either fixed immediately under tension for electron microscopy, or were stimulated in a papillary muscle bath and then fixed for electron microscopy.

Control muscles were essentially normal. Shock muscles contained numerous lesions. Comparison was made between the ultrastructural characteristics

of myocardial zonal lesions and myofibrillar degeneration in the shock muscles. The results are presented in tabular form, and the morphologic and etiologic differences between these lesions are discussed.

It is clear that the two types of lesions are distinctly different both morphologically and etiologically. However, they have often been confused in the literature; the object of this paper is to lessen that confusion. Failure to recognize and distinguish between these lesions can only impede experiments aimed at understanding the nature of the cardiac injury which is sustained in hypovolemic shock.

14. Alterations in pancreatic acinar cell organelles during circulatory shock. B. L. Herlihy and A. M. Lefer. Circ. Shock 2: 143-153, 1975.

Splanchnic artery occlusion (SAO) shock is a lethal form of circulatory shock. The pancreas produces significant quantities of toxic factors such as a myocardial depressant factor (MDF). Chronic ligation of the pancreatic ducts prevents MDF formation and enhances survival. Duct ligation also alters the activity and distribution of the lysosomal, zymogenic, and mitochondrial subcellular organelles. The mechanism whereby pancreatic duct ligation confers protection in SAO shock involves pancreatic acinar cell atrophy to the extent that only small amounts of MDF are produced. However, the mechanism of protection may also be related to a specific change in one or more of the intracellular organelles of pancreatic acinar cells, particularly the lysosomes and zymogen granules. Cats with ligated pancreatic ducts respond differently from nonligated cats to SAO shock in several respects. The cathepsin D activity of the large granule fraction of the ligated pancreas exhibits activities comparable to those observed in the nonshocked cat. Also, the duct-ligated pancreas does not demonstrate a loss of amylase activity in response to SAO shock as nonligated cats usually do. The data presented in this study indicate that pancreatic subcellular organelles may play an important role in the development of the shock state and that modification of pancreatic acinar cells by chronic pancreatic duct ligation can significantly prevent the autolytic response of these cells.

15. Humoral deficiency and reticuloendothelial depression after traumatic shock. J. E. Kaplan and T. M. Saba. Am. J. Physiol. 230: 7-14, 1976.

Circulating opsonin levels and reticuloendothelial (RE) phagocytic activity were investigated in anesthetized rats subjected to Noble-Collip drug (NCD) trauma. Reticuloendothelial function was assessed by colloid clearance kinetics and circulating opsonin levels by in vitro tissue slice bioassay. After sublethal shock, both hepatic RE phagocytosis and plasma opsonic activity were significantly ($p<0.001$) depressed in the 0.5- to 6-h post-trauma period. Pulmonary and bone marrow localization of the blood-borne test microparticles significantly ($p<0.05$) increased during hepatic RES depression. Hepatic RE cells from animals during the interval of post-traumatic in vivo phagocytic depression exhibited normal phagocytosis when incubated in normal pretrauma plasma and decreased phagocytic activity when incubated in posttrauma plasma. After sublethal shock, restoration of opsonin levels by 24 h after shock resulted in hepatic RE recovery.

Plasma opsonin levels declined in direct relationship to the degree of trauma. Progressive heaptic RE failure was correlated with the progressive decline in circulating plasma opsonic activity. The findings indicate that opsonic depletion may be involved in the etiology of hepatic reticuloendothelial depression after traumatic shock.

16. Insulin removal by isolated perfused rat liver. R. I. Misbin, T. J. Merimee, and J. M. Lowenstein. Am. J. Physiol. 230: 171-177, 1976.

Removal of unlabeled insulin was studied in the perfused rat liver. Insulin removal followed first-order kinetics over the range of concentrations found in the portal vein of postabsorptive rats, but deviated from first-order kinetics in experiments with a wider concentration range. Clearance was more than twice as great at concentrations normally found in the portal vein in the postabsorptive state (0.40-1.1 nM or about 60-100 μU/ml) than at concentrations expected after pancreatic stimulation (4.5-7.0 nM). Saturation of the liver's capacity to remove insulin, however, was not observed even at higher levels. Insulin clearance diminished when the flow rate was reduced. It was not significantly altered by prolonged starvation. Our results suggest that when the insulin concentration is high a greater percentage escapes hepatic degradation than when it is low. Hepatic insulin clearance is in part dependent on the portal flow rate. The kinetics of insulin removal by the perfused liver cannot be accounted for by the properties of insulin-degrading enzymes described by others.

17. Effect of antilymphocyte serum (ALS) on shock in rats. D. A. Ringle and B. L. Herndon. Am. J. Physiol. 230: 178-187, 1976.

Effects of treatment with rabbit anti-rat anti-lymphocyte serum and globulin (ALS and AGL) on shock survival were studied in Sprague-Dawley derived male rats. Because of their known cytotoxic capability, it was postulated that lymphocytes might play a role in the pathogenesis of shock and that suppression of lymphocyte function by ALS-ALG treatment should then protect against shock. Shock models used were tourniquet, endotoxin, and hemorrhagic shock. Protection against tourniquet shock was found for ALS made against thymocytes but not for ALS against spleen cells or lymph node cells. The shock-protective factor was found in the ALG-containing serum fraction but not in the primarily albumin fraction. No significant protection was found for ALS treatment against either endotoxin or hemorrhagic shock. ALS effects on blood cell counts, reticuloendothelial system clearance, and inflammation were studied to help identify effects of ALS on shock survival. It was concluded from these studies that thymic or thymus-processed lymphocytes could play a role in the pathogenesis of shock but that multiple effects of ALS/ALG treatment necessitate further studies to elucidate any role for lymphocytes in shock.

18. The metabolic events of starvation. C. D. Saudek and P. Felig. Am. J. Med. 60: 117-126, 1976.

Considering the total calories available to the normally fed man, there is fuel enough to last more than 80 days, even assuming utilization of 2,000 calories/day. E. F. DuBois, Professor of Medicine and Physiology at Cornell, likened the distribution of these stored calories to three shipboard lockers.

Eighty-five % of the available calories are in the fat locker. This maximizes efficiency, adipose tissue having very little intracellular water and thus having the most calories per gram of tissue. Other storage forms are hydrophilic, requiring intracellular water for solubilization and thus reducing the calories available per gram of tissue.

Protein provides about 14% of the available potential calories, but protein has vital enzymatic, structural and mechanical roles. Dipping into this locker as a source of fuel is done at great cost to the organism. We will be considering in detail the metabolic gymnastics by which the body avoids burning protein during starvation.

Carbohydrate, the remaining storage form, is a small locker, consisting primarily of about 75 g of liver glycogen. Muscle glycogen is not available for direct glucose production, because muscle lacks glucose-6-phosphatase. Benedict's study of his subject demonstrated by respiratory quotient measurements that carbohydrate is a significant energy source only in the first few days of fasting. The rapid depletion of liver glycogen has since been well documented.

19. Digitalis: A neuroexcitatory drug. R. A. Gillis, D. L. Pearle, and B. Levitt. Circulation 52: 739-742, 1975.

Appreciation for the important neural role in the cardiovascular effects of digitalis suggests several directions for future research. First, although no major differences among digitalis compounds has yet been documented (except for pharmacokinetics), such differences may exist in their neural activation. Recent evidence suggests that digitalis compounds differ in the relative role of the sympathetic nervous system in their cardiotoxicity, and in their capacity to activate the parasympathetic nervous system. Second, the role of the sympathetic nervous system in digitalis cardiotixicity suggests new therapeutic modalities. One approach that has been effective experimentally is the use of central nervous system depressants to counteract digitalis-induced ventricular arrhythmias. Third, since central nervous system activation seems important, and perhaps even causative in digitalis cardiotoxicity, new digitalis derivatives which do not cross the blood-brain barrier might be found which would retain direct inotropic properties without electrophysiologic toxicity.

20. Malnutrition in cardiac surgical patients. Results of a prospective, randomized evaluation of early postoperative parenteral nutrition. R. M. Abel, J. E. Fischer, M. J. Buckley, G. O. Barnett, and W. G. Austen. Arch. Surg. 111: 45-50, 1976.

A randomized evaluation of 44 malnourished patients, wherein 24 were used as controls and 20 received immediate postoperative parenteral hyperalimentation, indicated that five days of nutritional therapy had no notable effect on the morbidity and mortality experienced by the malnourished patients, in comparison to a third, nonmalnourished group of similar patients. Although central venous nutrition was safely administered without complications immediately after cardiac operations, clinical efficacy of this therapy could not be demonstrated. The inability to

establish a dose-response relationship, and hence administer the "optimum" amount of nutrients, may have accounted for the negative results reported. Although preoperative malnutrition is associated with a poorer result after cardiac surgery, postoperative repletion of nutrients appears to be ineffective in reversing this relationship.

21. Aspirin and myocardial infarction. H. Jick. Am. Heart J. 91:126, 1976.

Acetyl salicylic acid (aspirin) has a marked and prolonged inhibitory effect on platelet aggregation. Aggregation to collagen is abolished, as is the secondary wave of aggregation to adenosine diphosphate (ADP). This latter probably represents the release of endogenous ADP from the platelets themselves and when it occurs aggregation is irreversible.

Platelets are believed to play a key role in thrombosis. There is, therefore, a growing interest in aspirin, and other drugs with an effect on aggregation, as possible preventive measures in thromboembolic conditions.

22. Myocardial contractile force as a function of coronary blood flow. J. M. Downey. Am. J. Physiol. 230: 1-6, 1976.

The contractile force of the deep and superficial myocardial fibers was examined in the open-chest anesthetized dog as a function of coronary blood flow (CBF). When 1) dogs that failed to demonstrate coronary autoregulation were eliminated from the data base and 2) CBF and contractile force data were both normalized as a percent of their values when perfusion was from aortic pressure (autoperfusion), the relationship between them became very reproducible. Contractile force was highly dependent on the flow rate when the CBF was below that chosen by autoregulation (the rate during autoperfusion). Conversely contractile force was relatively independent of flow at higher CBF. The contractile force-CBF curve thus was found to break precisely at the autoperfused CBF. When myocardial metabolism was elevated by paired electrical stimulation this relationship was unchanged. It was concluded that coronary blood flow is tightly regulated to match metabolic needs over a range of metabolic rates.

23. Use of chloroquine in shock. C. E. Famewo, W. H. Noble, and M. B. Garvey. Canad. Anesth. Soc. J. 22: 687-695, 1975.

Manu studies have been done by different investigators on drugs that affect platelet adhesion and aggregation. The ideal drug should be readily available, rapidly effective, relatively cheap and should not cause increased bleeding. This study was done as a continuation of the search for drugs that inhibit platelet aggregation, so reducing the increase in pulmonary vascular resistance and lung water following haemorrhagic shock. This paper reports the authors' results with Chloroquine, an antimalarial drug.

One group of dogs received single doses of intramuscular chloroquine and another group served as a control. The dogs were subjected to haemorrhagic shock and then retransfused with their own blood after 2 hr of shock. The chloroquine-treated dogs had normal PA pressures after correction of acidosis and significantly smaller increases in the pulmonary vascular resistance. The results are similar but less marked than those obtained with aspirin. Chloroquine inhibited in vitro platelet aggregation by 50% and was not associated with any increased bleeding. This may be an

advantage when used in patients with multiple trauma or increased bleeding tendency.

24. Digitalis after two centuries. D. G. Friend. Arch. Surg. 111: 14-19, 1976.

It is the bicentennial anniversary of the introduction of digitalis into medicine. Digitalis is one of the most important drugs ever discovered, and after two centuries, it is still the most widely used drug in cardiology. However, it was at one time so badly abused that for nearly a century it was almost abandoned. Early in this century, the valuable effects of digitalis were once again recognized and extended. The molecular basis of action has been defined and now methods are available to detect early toxicity. Recent advances in combating toxic effects show considerable promise. Skillful administration of the drug, using purified standard tablets, careful monitoring by clinical electrocardiography, and analytical methods can secure the maximum benefits with the minimum degree of toxicity.

25. The effects of coronary vasodilatation on cardiac performance during endotoxin shock. M. D. Peyton. Experimental Myocardial Infarction: New Aspects of Trasylol Therapy, Internat. Symposium, Vol. 8. F. K. Schattauer Verlag, N.Y., 1975, pp. 289-291.

Recent studies in our laboratories have demonstrated significant failure in the isolated canine heart confronted with endotoxin and lowered coronary arterial perfusion pressure. In order to perhaps better understand the mechanism of the failure and to pursue a mode of therapy, the effects of coronary vasodilatation by infusion of sodium nitroprusside were studied in this model. With these initial studies a definite beneficial effect of coronary vasodilatation has been observed during endotoxin shock. The potential use of such therapy warrants further studies with emphasis on evaluating the hemodynamics of the intact animal.

26. Myocardial function during lowered and risen coronary perfusion: Effects of coronary hypotension and endotoxin on myocardial performance. L. B. Hinshaw, L. T. Archer, J. J. Spitzer, M. R. Black, M. D. Peyton, and L. J. Greenfield. Experimental Myocardial Infarction: New Aspects of Trasylol Therapy, Internat. Symposium, Vol. 8, F. K. Schattauer Verlag, N.Y., 1975, pp. 271-280.

The purpose of the present study was to explore the separate roles of aortic hypotension and endotoxin in the pathogenesis of heart failure. Experiments were performed on isolated canine hearts supported by blood from anesthetized animals. The first series of hearts (experimental group) was subjected to 4 hr of coronary hypotension plus endotoxin administered to both heart and support dog, while the second series (control group) was subjected to low pressure alone. Approximately 90% of experimental hearts and 40% of the controls demonstrated dysfunction at 4 hrs, as evidenced by increased left ventricular end diastolic pressure at afterloads between 50 and 125 mm Hg. Negative dP/dt (-dP/dt) became less negative in experimental hearts at 4 hours while coronary blood flow, heart rate and oxygen uptake were elevated in relation to the control group. Myocardial efficiency decreased by 4 hrs in all hearts exhibiting failure. Findings suggest that early abnormal diastolic filling and inadequate coronary perfusion may perform significant roles in the precipitation of heart dysfunction after endotoxin.

27. Mechanisms of cardiac dysfunction in decreased coronary pressure: Effects of coronary hypotension on myocardial substrate utilization. J. J. Spitzer, A. A. Bechtel, L. T. Archer, M. R. Black, L. J. Greenfield, and L. B. Hinshaw. Experimental Myocardial Infarction: New Aspects of Trasylol Therapy, Internat. Symposium, Vol. 8. F. K. Schattauer Verlag, N.Y., 1975, pp. 281-287.

Changes in myocardial substrate utilization were studied following experimental coronary hypotension in the isolated heart of a small dog perfused with the blood of a large donor animal. Following a control period (100 mm Hg) the afterload of the isolated heart was adjusted to 50 mm Hg and kept at that level for 4 hrs. At the end of this experimental period, a second control was established at 100 mm Hg afterload. Coronary sinus blood flow and oxygen consumption decreased during hypotension and returned to normal during the second control period. Myocardial FFA uptake and oxidation did not change significantly. Lactate uptake was diminished during hypotension and the percentage of CO_2 derived from myocardial lactate utilization was also decreased. These changes were not present during the second control period. Glucose uptake was also diminished during hypotension as was the myocardial RQ. Half of the hearts exhibited elevated end diastolic pressure following hypotension. However, no metabolic differences were detectable between the failing and non-failing hearts. Thus, prolonged severe hypotension caused a decreased coronary sinus blood flow and myocardial oxygen consumption as well as a relative preference of FFA oxidation and diminished lactate and glucose uptake by the myocardium. It is concluded that the changes of myocardial substrate utilization were quite different following prolonged coronary hypotension from those obtained during experimental hemorrhagic or endotoxic shock.

28. Targets of endotoxin action. R. I. Walker. Milit. Med. 141: 97-99, 1976.

From the foregoing it can be seen that endotoxin elicits a cascade of ultimately lethal events through interactions at two levels. First, the toxin interacts with components of the host's immunologic defenses (i.e., complement, leucocytes, macrophages, etc.). Normally reactions to small amounts of endotoxin may be tolerated by the body, and these minor lesions are necessary for maintaining resistance to infection. Overwhelming endotoxin challenge would increase amounts of deleterious byproducts of the endotoxin-immunologic defense system interactions and, thus, contribute to mortality. The importance of regulating amounts of factors interacting with endotoxin is apparent in studies involving therapeutic treatment of endotoxemia, by means such as decomplementation or inducing thrombocytopenia.

The second level of endotoxin interaction is through incorporation of hydrophobic portions of the LPS molecule into lipid-rich cell membranes. The importance of such interactions is probably governed by which tissues are exposed to the endotoxin and, possibly, to the lipid composition of the cell membranes. One avenue of therapeusis, therefore, may be directed toward the use of inhibitors which could bind to the hydrophobic portions of endotoxin.

29. Effects of allopurinol on hepatic adenosine nucleotides in hemorrhagic shock. R. W. Hopkins, J. Abraham, F. A. Simeone, and C. A. Damewood. J. Surg. Res. 19:381-390, 1975.

From the present studies, it is reasonable to conclude that pretreatment with allopurinol facilitates the restoration of the concentration of energy-rich adenosine nucleotides when blood is reinfused after a period of oligemia. Substrates for the resynthesis of ATP are made available by preventing the irreversible breakdown of hypoxanthine. Pretreatment, however, does not prevent the fall in concentration of adenosine nucleotides during oligemia. If the ATP deficiency during the period of oligemia and prior to reinfusion is overly prolonged, it is possible that cellular and tissue death from lack of a source of energy may proceed to the point of making recovery impossible despite reinfusion and subsequent availability of ATP.

30. Levels of allantoin and uric acid in dogs subjected to hemorrhagic shock. F. A. Simeone, J. Abraham, R. W. Hopkins, and C. A. Damewood. J. Surg. Res. 19: 373-380, 1975.

The changes in concentration of uric acid and of allantoin were studied in the blood and lymph of mongrel dogs in experimental hemorrhagic shock under sodium pentobarbital anesthesia. The object of the experiment was to determine whether the rise in uric acid concentration in experimental shock results from increased breakdown of adenosine and guanosine nucleotides or from failure of the hepatic conversion of uric acid to allantoin.

The concentration of uric acid in serum and lymph was significantly higher in the dogs that were bled than in those serving as controls. The rate of conversion of uric acid to allantoin during oligemia did not change significantly in these dogs. After the return of reservoir blood to the animals, the concentration of allantoin in serum and lymph thus results from an increased degradation of the adenosine and guanosine nucleotides, and not from failure of conversion of uric acid to allantoin in the liver.

31. Histamine (First of two parts). M. A. Beaven. New Engl. J. Med. 294: 30-36, 1976. (For review of second part, see ref. #67.)

Although the early research gave an indication of the possible involvement of histamine in inflammatory and anaphylactic reactions and in gastric secretion, subsequent research, for the most part, provided little additional information on its participation in these processes. In the past few years, however, there has been renewed interest in histamine because of the following three important developments: the discovery of a new group of antihistamines that block specifically actions of histamine (for example, gastric secretion) not blocked by the older classic antihistamines; the finding that antigen-induced release of histamine from basophils and tissue mast cells is mediated by IgE (reaginic) antibody and that this release is modulated by catecholamines, cholingergic agents, and histamine through alteration in the intracellular levels of cyclic nucleotides; and, lastly, the development of a sensitive and specific isotopic assay of histamine that permits its measurement in plasma and tissue fluids. This article outlines the earlier work on histamine and reviews these recent developments.

32. Endotoxin in cerebrospinal fluid. Detection in neonates with bacterial meningitis. G. H. McCracken, Jr., and L. D. Sarff. J. Am. Med. Assoc. 235: 617-620, 1976.

The Limulus lysate assay was used to measure endotoxin in 307 cerebrospinal fluid (CSF) specimens from 84 infants with meningitis caused by gram-negative bacteria. Endotoxin was detected in 117 CSF samples (33%), and its presence was correlated with recovery of bacteria from CSF cultures. A direct relationship was demonstrated between the presence, persistence, and concentration of endotoxin in CSF and outcome from meningitis. Measurement of CSF endotoxin by the Limulus assay and of CSF K_1 antigen by counterimmunoelectrophoresis (CIE) showed a significant correlation between the presence and amount of these two Escherichia coli K_1 capsular substances. Endotoxin was detected in 72% of infants, and 52% had K_1 antigen in CSF specimens obtained within 24 hours of diagnosis. Combining the results of the Limulus assay and CIE, 81% of patients with E. coli K_1 meningitis had endotoxin or K_1 or both in initial CSF samples.

33. Glucocorticoid effect on hepatic carbohydrate metabolism in the endotoxin-shocked monkey. J. J. Schuler, P. R. Erve, and W. Schumer. Ann. Surg. 183: 345-354, 1976.

This study investigated the effect of glucocorticoid treatment on survival, on hepatic carbohydrate metabolism, and on levels of hepatic adenine nucleotides in the endotoxin-shocked monkey. Dexamethasone sodium phosphate (DMP) administered either at the time of endotoxin challenge or up to 90 minutes afterward significantly increased the survival rates. Endotoxin administered alone significantly decreased the hepatic levels of glucose-6-phosphate, fructose-6-phosphate, phosphoenolpyruvate, adenosine triphosphate, adenosine diphosphate, and glycogen; and it significantly increased the hepatic levels of fractose-1,6-diphosphate, lactate, and adenosine monophosphate. The administration of DMP at the time of endotoxin challenge maintained the levels of all these metabolites at or near the control levels.

34. Why control blood glucose levels? A. A. Rossini. Arch. Surg. 111: 229-233, 1976.

The controversy as to the relationship between the degree of control of diabetes and the progression of the complications of the disease has not been resolved. However, in this review, various studies suggesting a relationship between the metabolic abnormality and the diabetic complications are examined. The disadvantages of the uncontrolled diabetes mellitus can be divided into two major categories--short-term and long-term. The short-term disadvantages of uncontrolled diabetes mellitus include the following: (1) ketoacidosis and hyperosmolar coma; (2) intracellular dehydration; (3) electrolyte imbalance; (4) decreased phagocytosis; (5) immunologic and lymphocyte activity; (6) impairment of wound healing; and (7) abnormality of lipids. The long-term disadvantages of uncontrolled diabetes mellitus include the following: (1) nephropathy; (2) neuropathy; (3) retinopathy; (4) cataract formation; (5) effect on perinatal mortality; (6) complications of vascular disease; and (7) the evaluation of various clinical studies suggesting the relationship of elevated blood glucose levels and complications of diagetes mellitus. It is suggested that until the question of control can absolutely be resolved, the recommendation is

that the blood glucose levels should be controlled as close to the normal as possible.

35. Insulin response to glucose in hypermetabolic burn patients. D. W. Wilmore, A. D. Mason, Jr., B. A. Pruitt, Jr. Ann. Surg. 183: 314-320, 1976.

Fifty-four intravenous glucose tolerance tests were performed in 12 normal individuals and 21 thermally injured patients. In the 17 hypermetabolic burn patients studied between the 6th and 16th days postinjury, fasting blood glucose was elevated (111±7 mg/100 ml, mean±SE compared to 85±3 in controls, $P<0.001$), but the instantaneous proportionality constant for glucose disappearance (k) was similar to that obtained in normal individuals (5.27±0.51, 100/min vs 4.01±0.58 in normals, NS). Fasting serum insulin concentrations were comparable in the 12 normals and 17 hypermetabolic burn patients (22±3 μU/ml in normals vs 22±2), as was fasting insulin corrected for fasting glucose (24±3 in normals vs 21±3, NS), initial insulin response (0-10 min delta insulin, 58±13 in normals vs 67±10, NS) or total insulin response corrected per unit glycemic stimulus (insulinogenic index, 0.48± 0.10 in normals vs 0.52±0.07, NS). With time following injury, the proportionality constant for glucose disappearance and insulin response decreased, and these alterations were related to the post-traumatic weight loss. In the 5 convalescent patients studied between the 37th and 90th days postinjury, glucose and insulin dynamics appeared similar to those observed in starved man.

In these burn patients, hypermetabolism and negative nitrogen balance occurred in association with a normal insulin response to glucose, Increased hepatic gluconeogenesis appears to be characteristic of the catabolic response to this stress, directed by increased glucagon and catecholamines, not a decrease in fasting insulin or dampened insulin response.

36. Studies on the subcellular pathophysiology of ischemia. B. F. Trump, W. J. Mergner, M. Won Kahng, and A. J. Saladino. Circulation 53 (Suppl. 1): I-17-I-26, 1976.

The loss of ability to synthesize adenosine triphosphate (ATP) by mitochondria in ischemic cells even in a favorable medium correlates with the loss of cell viability. The early lesion at the molecular level needs further investigation but appears to involve an increased permeability of the mitochondrial membrane possibly promoting proton leak and obviating oxidative phosphorylation. The nature of this leak could involve changes in phospholipid-protein interactions, especially since the early release of free fatty acids and changes in phospholipid composition occur.

37. The effect of dopamine on renal microcirculation in hemorrhagic shock in dogs. B. Nagakawa, L. Goldberg, J. McCartney, and T. Matsumoto. Surg. Gynec. Obstet. 142: 871-874, 1976.

Dopamine, a naturally occurring catecholamine, was infused at the rate of 6 micrograms per kilogram per minute on an hemorrhagic shock model in dogs. Urinary output was continuously recorded, with arterial pressure being maintained at 50 mmHg. At the termination of the experiment, the dogs were sacrificed, and renal microcirculation was studied by an angiomicrohistologic technique.

There was a dramatic increase in urinary output following the infusion of dopamine. Results of the microcirculatory study of the renal vasculature showed markedly increased cortical perfusion and dilataion of vessels, particularly at a level of afferent arterioles; however, findings on efferent arterioles were inconsistent. Also, changes in the microvasculature of the medulla were less striking than those of the cortex following the administration of dopamine.

38. Physiopathologic responses of the rhesus monkey to live Escherichia coli. L. B. Hinshaw, B. Benjamin, L. T. Archer, B. Beller, J. J. Coalson, and J. G. Hirsch. Surg. Gynec. Obstet. 142: 893-900, 1976.

The present study was designed to develop an animal model applicable to the clinical patient in the investigation of the pathogenesis of septic shock. The model currently described is a lightly anesthetized, unrestrained monkey, carefully monitored during a 24 hr observation period. Varying doses of live Escherichia coli organisms were infused intravenously during a 30 min period, and a variety of hemodynamic, respiratory and metabolic parameters were monitored. Doses of organisms varied between 7.6×10^9 and 3.0×10^{11} organisms per kg of body weight, and there was no obvious correlation between size of dose and survival time. Two of 9 experimental monkeys survived the Escherichia coli, while times of death of the remaining monkeys varied between 3 and 27 hours. Two control monkeys, not administered organisms, survived the 24 hr period with minimal changes in all measured parameters. Results reveal two patterns in response to organism administration. These were early acute death, after 3-4 hrs, and prolonged life, death after 20-27 hrs. The acute response was characterized by marked systemic hypotension, hypoglycemia, hypoinsulinemia, increased lactate level, decreased pH or respiratory depression. The other type of response involved profound sustained hypotension with hypoglycemia and hypoinsulinemia in most monkeys and elevations in lactate, blood urea nitrogen, potassium, creatinine, serum glutamic-oxalacetic, lactic dehydrogenase and fractionated-lactic dehydrogenase levels. Depressions in respiration were not evident in the group which survived a longer period of time. Renal fibrin thrombi, prominent in baboons administered Escherichia coli, were absent in the rhesus monkey regardless of the size of the dose of organisms. The results of this study suggest the operation of a multifactorial mechanism in septic shock with interactions between hemodynamic and metabolic factors varying within the species.

39. The effect of glucose infusion on selected hemodynamic and metabolic variables and on plasma insulin concentration in dogs after Escherichia coli endotoxin administration. J. J. Spitzer, G. G. Wagner, and W. G. Blackard. Circ. Shock 3: 31-38, 1976.

Selected hemodynamic and metabolic parameters were investigated in conscious nonanesthetized dogs after the administration of Escherichia coli endotoxin. In another group of dogs the hypoglycemia that develops after endotoxin administration was counteracted by the infusion of hypertonic glucose solution. No differences were observed in arterial pressure, heart rate, rectal temperature, pH, and hematocrit between the two groups of dogs in the course of the experiments. Cardiac output decreased less in the animals receiving glucose. Hypoglycemia was commonly found several hours after the administration of endotoxin in dogs not given glucose. Arterial lactate and O_2 concentrations were not different in the two

groups of dogs, nor was total body O_2 consumption. Free fatty acids (FFA) decreased more in the glucose-infused dogs. Five-hour survival was improved in the glucose-infused group, but survival by the next morning was not different between the two groups. Six of the 8 dogs given glucose after endotoxin administration showed extreme sensitivity to the glucose stimulus manifested by very high concentrations of plasma insulin in the subacute (3-5 hrs postendotoxin) phase of shock. Further studies are underway to characterize the hypersensitivity of the pancreatic beta cells to glucose after endotoxin.

40. Glucocorticosteroid therapy: Mechanisms of action and clinical considerations. A. S. Fauci (Moderator); D. C. Dale and J. E. Balow (Discussants)--NIH Conference. Ann. Int. Med. 84: 304-315, 1976.

The administration of glucocorticosteroid results in a wide range of effects on inflammatory and immunologically mediated disease processes. Glucocorticosteroids cause neutrophilic leukocytosis together with eosinopenia, monocytopenia, and lymphocytopenia. A principal mechanism whereby corticosteroids suppress inflammation is their impeding the access of neutrophils and monocytes to an inflammatory site. Granulocyte function is relatively refractory, whereas monocyte-macrophage function seems to be particularly sensitive to corticosteroids. Corticosteroid administration causes a transient lymphocytopenia of all detectable lymphocyte subpopulations, particularly the recirculating thymus-derived lymphocyte. The mechanism of this lymphocytopenia is probably a redistribution of circulating cells to other body compartments. There is considerable disagreement about the direct effects of corticosteroid administration on human lymphocyte function. The corticosteroid regimen should be adjusted to attain maximal therapeutic benefit with minimal adverse side effects. Often, alternate-day dosage regimens effectively maintain disease remission with minimization or lack of Cushingoid and infectious complications.

41. Estimation of glucose turnover and recycling in rabbits using various [^{3}H, ^{14}C] glucose labels. A. Dunn, J. Katz, S. Golden, and M. Chenoweth. Am. J. Physiol. 230: 1159-1162, 1976.

The glucose replacement rate, percent carbon recycling, mean glucose transit time, and the glucose mass were determined in fasted unanesthetized rabbits after administration of [2-^{3}H,U-^{14}C]-, [3-^{3}H,U-^{14}C]-, [5-^{3}H,U-^{14}C]- or [6-^{3}H,U-^{14}C] glucose using the procedures of Katz et al. The glucose replacement rates and carbon recycling determined with [2-^{3}H, U-^{14}C] and [5-^{3}H,U^{14}C] glucose are equivalent and greater than those obtained with [3-^{3}H,U^{14}C]- and [6-^{3}H,U-^{14}C] glucose. Although the means of the glucose replacement rates and percent carbon recycling obtained using [3-^{3}H,U-^{14}C]- and [6-^{3}H,U-^{14}C] glucose are similar, greater variation resulted using the former tracer. Comparisons of detritiation rates and percent carbon recycling using [2-^{3}H,U-^{14}C]- and [6-^{3}H,U-^{14}C] glucose suggest that about 10% of tritium is lost from carbon 2 via futile cycling at the glucose 6-phosphate level. Similarly, comparisons of [5-^{3}H,U-^{14}C]- and [6-^{3}H,U-^{14}C] glucose metabolism suggest that about 10% of tritium lost from carbon 5 occurs via futile cycling at the fructose diphosphate level and/or via the transaldolase reaction. Our results indicate that [6-^{3}H,U-^{14}C] glucose is the more suitable tracer for determining the glucose replacement rate and carbon recycling in vivo.

42. Hemodynamic alterations in splanchnic arterial occlusion shock and the effects of dexamethasone sodium phosphate. R. D. Goldfarb and T. M. Glenn. Circ. Shock 2: 287-299, 1975.

The ability of dexamethasone sodium phosphate (DSP) to modify cardiac performance and the biochemical alterations associated with splanchnic artery occlusion (SAO) shock was investigated. Dexamethasone (5 mg/kg, iv) or placebo was infused 30 min before subjecting dogs to lethal SAO shock and again before (lo-15 min) release of the occlusion. Left ventricular function curves were performed before SAO, before release of the occlusion, and 30 min postrelease. There was no evidence of a direct positive inotropic effect of DSP in sham shocked dogs. However, a marked depression in peak cardiac work was noted in placebo-treated shocked dogs (35% decrease, postrelease) as well as a significant decrease in dP/dt, an index of cardiac contractility. In shocked dogs treated with the steroid there was no significant depression in cardiac work or dP/dt. After release of the occlusion, the aortic flow of DSP- and placebo-treated shocked dogs exhibited qualitatively similar decreases; however, the response was significantly less sustained in DSP-treated dogs. Further, splanchnic tissues of DSP-treated shocked dogs showed a significantly higher degree of lysosomal stability compared with tissues from placebo-treated shocked dogs. In addition, plasma levels of myocardial depressant factor (MDF), a cardiotoxic peptide, were lower in DSP-treated shocked dogs than in placebo-treated shocked animals. The maintenance of cardiac performance in DSP-treated shocked animals correlated with the failure of these animals to exhibit significant increases in plasma MDF and free splanchnic lysosomal enzyme activities. Thus, DSP may exert its protective action on cardiac function in SAO shock indirectly by preventing the disruption of lysosomal membranes, the release of lysosomal acid proteases, and the subsequent formation of the cardiodepressant peptide, MDF.

43. Alteration of canine renal vascular response to hemorrhage by inhibitors of prostaglandin synthesis. J. L. Data, L. C. T. Chang, and A. S. Nies. Am. J. Physiol. 230: 940-945, 1976.

The involvement of prostaglandins in the redistribution of renal cortical blood flow to inner cortical nephrons during hemorrhagic hypotension was studied in the pentobarbital-anesthetized dog. Total renal blood flow and distrubiton of renal cortical flow were determined with the radioactive microsphere technique by dividing the cortex into four zones of equal thickness, zone 1 being outermost and zone 4 being juxtamedullary. Two inhibitors of prostaglandin synthesis were used: indo thacin 8 mg/kg and aspirin 100 mg/kg. The inhibitor or the vehicle was given intravenously prior to a control period which was followed by a hemorrhage sufficient to decrease arterial pressure by about one-third. The distribution of cortical flow was determined before hemorrhage, during hemorrhagic hypotension, and after transfusion. In the vehicle-treated dogs, total renal blood flow was well maintained, but flow redistributed to favor thd inner cortical nephrons. This vasodilation in the inner cortex was blocked by both inhibitors of prostaglandin synthesis resulting in a decrease in total renal blood flow and relative ischemia of the juxtamedullary nephrons. Salicylate levels required to accomplish blockage

of inner cortical vasodilation were less than 7 mg/100 ml. These studies indicate that prostaglandins are responsible for the decreased vascular resistance of the inner cortical nephrons which results in the redistribution of blood flow during hemorrhage, and when prostaglandin synthesis is blocked, the kidney vasculature constricts during hemorrhage.

44. Cerebral hemodynamics during endotoxin shock in the dog. T. E. Emerson, Jr. and J. L. Parker. Circ. Shock 3: 21-30, 1976.

Cerebral hemodynamics were monitored before and for 4 hrs of gram-negative endotoxin shock in the dog. Shock was associated with an early reduction of cerebral blood flow to 63% of control on the average, which decreased further to 39% of control by the 4th hour of shock. A fall in cerebral perfusion pressure was responsible for the early decrease in flow. However, the subsequent decrease in blood flow was due to a progressive increase in cerebral vascular resistance, which became statistically significant at the 4th hour of shock. This paradoxical increase in resistance occurred in the face of arterial hypotension, acidosis, hypoxia, and normocapnia. These data show that the cerebral blood flow is compromised in the dog during endotoxin shock, which may contribute to a condition of cerebral ischemia.

45. Endotoxin shock: The effect of disodium cromoglycate on plasma histamine concentrations. J. K. Rupnik, I. D. Wells, and F. L. Glauser. Circ. Shock 3: 45-53, 1975.

In an attempt to define the role of endogenously released histamine in the shock associated with endotoxemia, we studied four groups of dogs and measured changes from baseline in blood pressure (BP), blood lactate, and plasma histamine concentrations hourly for 5 hrs after the intravenous injection of saline solution (group I, 3 dogs); 2 to 2.5 mg/kg of disodium cromoglycate (DSCG, group II, 5 dogs); 2.5 to 3 mg/kg of Escherichia coli endotoxin (group III, 8 dogs) and 2 to 2.5 mg/kg of DSCG prior to 2.5 to 3 mg/kg of endotoxin (Group IV, 9 dogs). In group I and group II animals there was no statistically significant change in any of the parameters over the 5 hrs (although in group II, BP decreased slightly (9.2±4.4%) during the 1st 2 hrs); plasma histamine concentrations increased slightly during the 1st 3 hrs (11.2±3.2%) and lactate concentrations increased during the 1st 2 hrs (15.5±7.7%). In contrast, group III animals had a marked decrease in BP at all sample hours with a mean of 42.3±3.1% and a marked increase in plasma histamine concentrations (mean of 324±26.9%) and lactate concentration (mean of 166.2±30.1%). Group IV animals had a similar decrease in BP (mean of 41.6±3.0, not significant (NS) compared with group III) and increase in lactate concentration (220.5±27.7%, NS), but the histamine concentration increase was markedly blunted (101.2± 15.5%, $p<0.001$) when compared with group III. We conclude that DSCG decreases venous histamine levels in experimental endotoxin shock but does not affect the shock parameters (BP, blood lactate concentrations).

46. A clinicopathologic study of hepatic dysfunction following shock. H. R. Champion, R. T. Jones, B. F. Trump, R. Decker, S. Wilson, M. Miginski, and W. Gill. Surg. Gynec. Obstet. 142: 657-663, 1976.

Nineteen patients who had profound hypotensive shock were studied to correlate the light and electron microscopic appearances of the liver with the clinical and biochemical evidence of hepatic dysfunction. Despite the multiple etiologic factors that can result in jaundice in these patients, a fluctuating pattern occurs which enables the correlation of a bilirubin peak with the predominating etiologic factor. Immediately after shock, there was enzymatic and light and electron microscopic evidence of hepatocellular damage, resulting in a jaundice peak on the 8th to 10th day after the shock episode. This was followed by repair and regeneration of the liver as well as an increase in cholestatic enzyme levels. Later, bilirubin peaks occurred when hepatocellular function was further decreased or overloaded against this background of dysfunction related to the episode of shock.

Recovery of hepatic function could continue or be delayed by intercurrent disease, particularly systemic infection. Support of hepatic function, similar to that available for pulmonary and renal failure may, in the future, be used to effect the prognosis of these patients.

47. Mechanical and humoral factors affecting cardiac function in shock. D. David and S. Rogel. Circ. Shock 3: 65-75, 1976.

Hypovolemic shock was produced in open chest dogs in which the ascending aorta was constricted to a degree such as to maintain intracardiac, proximal aortic, and coronary artery pressures at the control level, while cardiac output and coronary blood flow were kept at the preshock level by increasing venous return. In this experimental model the dog was in deep shock except for the heart, which was required to perform as in the control state but was perfused with blood returning from the shocked body. It was found that under these circumstances shock could be maintained for 6-10 hours but release of the aortic constriction and reinfusion of the shed blood was followed by rapid fatal deterioration. Treatment with aprotinin, a protease inhibitor, did not change the course of the experiment significantly during the hemodynamic protection of the heart. Marked improvement in myocardial tension and performance was observed in the postreinfusion state, however, which was ascribed to the partial inhibition of a circulating cardiac depressing factor permitting better preservation of the contractile force of the heart during a state of hypovolemic shock.

48. Direct effect of endotoxin on the gastric mucosal microcirculation and electrical gradient. L. Y. Cheung, R. S. Reese, and F. G. Moody. Surgery 79: 564-568, 1976.

The effects of intra-arterial infusion of E. coli endotoxin at 1.0 mg/min on the gastric total and mucosal blood flows, electrical potential difference, and ionic fluxes across the gastric mucosa were studied in an exteriorized, chambered preparation of canine fundic stomach. Gamma-labelled microsphere technique was used in addition to venous drainage and plasma aminopyrine clearance for the measurement of total and mucosal blood flow, respectively. In spite of normal systemic blood pressure throughout the experiment, E. coli endotoxin infusion caused a significant

decrease in total gastric blood flow and in the fractional distribution of flow to the mucosae. There was no significant arteriovenous shunting of microspheres. Significant reduction in potential difference and hydrogen-ion back diffusion also was noted after endotoxin infusion, possibly as a consequence of reduced mucosal blood flow. The results indicate that significant gastric mucosal ischemia can occur and may represent a mechanism in the development of gastric erosions in endotoxemia, even in the absence of systemic hypotension.

49. Species differences in insulin secretory responses during hemorrhagic shock. J. M. Hiebert, C. Kieler, J. S. Soeldner, and R. H. Egdahl. Surgery 79: 451-455, 1976.

Insulin secretory rates (ISR) during intravenous glucose tolerance tests (IVGTT's) were measured in 6 dogs subjected to hemorrhagic shock and were compared to ISR's from 5 monkeys subjected to shock of comparable severity. ISR's also were measured in normotensive control dogs and monkeys subjected to the same blood sampling protocol. A sixfold increase in ISR occurred in shocked dogs after glucose loading; however, no ISR response occurred in monkeys subjected to hemorrhage. It is concluded that marked species differences exist in the insulin-glucose metabolic responses to shock. In addition, the dog would appear to be an inappropriate experimental animal as applied to trauma-insulin metabolism in man.

50. Tracheobronchial and pulmonary cytologic changes in shock. Z. Friedman-Mor, J. Chalon, J. S. Katz, F. Gorstein, H. Turndorf, and L. R. Orkin. J. Trauma 16: 58-62, 1976.

Smears were made from tracheobronchial washings of patients undergoing general endotracheal anesthesia for surgery. Morphologically abnormal histiocytes were noticed in specimens obtained from subjects during hemorrhagic shock. These cells were overloaded with Papanicolaou stain (a greenish orange compound) which compressed the nucleus against the cell membrane. Cytochemical staining methods were undertaken to discover the composition of this substance. In secretions suctioned from 10 patients in shock, large numbers of histiocytes were found to have ingested inorganic iron detectable by the Prussian blue method. Only two patients from a matched control group had smears in which this phenomenon was discovered. The maximum proportion of histiocytes containing Prussian blue granules was 40% for patients in shock and only 2% in normal controls.

Histologic studies conducted on rats submitted to hemorrhagic shock were carried out to investigate this phenomenon. Iron-laden histiocytes were found in the kidneys, spleen, and lungs of both shocked and control animals. However, substantially more histiocytes containing Prussian blue positive granules were discovered in the lungs of rats in shock than in controls. It may, therefore, be that iron is deposited in the lungs in low flow states.

51. Turnover of amino acids in sepsis and starvation: Effect of glucose infusion. N. Vaidyanath, G. Oswald, G. Trietley, W. Weissenhofer, E. Moritz, R. H. McMenamy, R. Birkhahn, T. F. Yuan, and J. R. Border. J. Trauma 16: 125-135, 1976.

The catabolism of glucose and amino acids has been studied in the normal, the fasted, and the fasted septic dog. The fasted septic dog oxidized

more glucose and alanine, and had more gluconeogenesis from alanine and the five tritiated amino acids--glutamate, threonine, phenylalanine, leucine, and valine--as compared to the normal and equally fasted dog. Thus the total body protein catabolic state was characterized in biochemical terms. In contrast, following glucose infusion, the fasted septic animal responded much like the fasted animal in terms of decreased amino acid gluconeogenesis and decreased plasma concentrations of amino acids, fats and fat products, but considerably increased the oxidation of alanine. The increased alanine oxidation appeared to be primarily related to increased tissue clearance and increased plasma concentration. There was some suggestive evidence for enhanced oxidation of the tritiated amino acids including leucine and valine during glucose infusion.

The protein catabolic state secondary to this sort of sepsis in dogs only on per os fluid support appears to be best characterized as a glucose catabolic state with alanine being oxidized directly. Such states are known to be ones of enhanced metabolic rate secondary to enhanced synthetic processes generally. This is probably related to enhanced sympathetic nervous system release of glucagon with insulin being normally responsive to glucose because of a normal plasma epinephrine.

52. Immunological reactions involving leukocytes: I. Detection of antibodies to human granulocytes by measurement of the metabolic events associated with phagocytosis. Y. R. Laleli, S. B. Bilezikian, M.-F. Tsan, B. A. Hodkinson, and P. A. McIntyre. J. Hopkins Med. J. 138: 43-47, 1976.

During phagocytosis, glucose oxidation via the hexose monophosphate shunt (HMS) is markedly stimulated in human polymorphonuclear leukocytes. A method is described for the detection of antibodies to human granulocytes which exploits this fact. The source of antibodies was rabbit antihuman leukocyte serum (RAHLS) obtained by repeated immunization of normal rabbits with human granulocyte homogenates. HMS activity was quantitated by measuring the release of $^{14}CO_2$ from glucose-1-^{14}C. Under precisely defined experimental conditions, RAHLS and its IgG fraction inhibited $^{14}CO_2$ release. The inhibitory effect of RAHLS on human granulocyte phagocytosis-associated HMS activity could be reduced by prior absorption of RAHLS with human granulocytes. Compared to the cytotoxic and leukoagglutination tests, this method appears more sensitive with respect to detection of xenogeneic antibodies to human granulocytes.

53. Transfusion of neutrophils as prevention or treatment of infection in patients with neutropenia. D. R. Boggs. New Eng. J. Med. 290: 1055-1062, 1974.

Treatment of life-threatening bacterial infections in patients with severe neutropenia is extraordinarily difficult, at least as judged by any degree of long-term success. Although factors other than neutropenia often contribute to the susceptibility of such patients to infection, there is little doubt that neutropenia per se is associated with a marked increase in the frequency and severity of infection. Since replacement of platelets by transfusion has proved beneficial in preventing and treating bleeding in patients with thrombocytopenia, it is natural that interest has grown in the possible prevention and treatment of infection in patients with neutropenia by transfusing neutrophils. Although clinical benefit has been suggested after neutrophil transfusion in infected neutro-

penic patients, such transfusions have not been used widely. The promise as well as the very appreciable problems associated with this experimental form of therapy will be reviewed.

The discussion of this article could be interpreted as suggesting that continued trials of neutrophil transfusion are questionable enterprises, but it is not this author's intent to present that discouraging a picture. Many of the problems can be solved by persistent and consistent developmental studies. Furthermore, a number of unknown areas relevant to neutrophil kinetics might indicate that a clinically useful neutrophil-transfusion program need not raise and maintain circulating neutrophils in the normal range. First of all, a number of patients with moderately severe neutropenia live for years without suffering serious infection. There is no well established level of blood neutrophils below which the overall function of the cellular system is impaired. There seems little question that large numbers of neutrophils are needed to combat existing infection. Indeed, complete eradication of infection in patients with neutropenia is unusual unless neutropenia is corrected. Little is known, however, about the number of neutrophils required to prevent infection, or, for that matter, the exact role that they have in preventing infection. Neutrophils can be found migrating to such body surfaces as the lumen of bronchi and gut, and it is generally assumed that they have a part in preventing infection of these surfaces. Although marrow and blood-neutrophil transit times ahve been well delineated, neutrophil survival in the normal "tissue" phase has not been studied carefully. However, the observation that labeled neutrophils appear in saliva almost as soon as they are released to the blood from the marrow, as well as the rapid appearance and turnover of neutrophils in exudates, suggests that "tissue" survival is short. Nonetheless, it is at least conceivable that periodic transfusion of neutrophils in an amount too small to maintain normal blood levels might still "saturate" essential tissue sites and serve to prevent infection.

54. Hypoglycemic activity of endotoxin. II. Mechanism of the phenomenon in BCG-infected mice. J. W. Shands, Jr., V. Miller, H. Martin, and V. Senterfitt. J. Bacteriol. 98: 494-501, 1969.

The mechanism of the hypoglycemic activity of endotoxin in hyperreactive BCG mice was investigated. The mechanism was found to be an inhibition of the synthesis of glucose from noncarbohydrate sources. The possibilities of an induced hypermetabolic state and an induced release of insulin in response to endotoxin as causes for the hypoglycemic response were essentially ruled out. In addition, no clear-cut evidence of an insulin-like action by endotoxin was found in the in vivo setting.

55. Histamine release in man. W. Lorenz. Agents and Actions 5: 402-416, 1975.

Histamine release in man could be demonstrated using the fluorometric histamine assay in plasma as a reliable test. Histamine release in animals may be relevant in some cases for human subjects, as shown for anaesthetic drugs and plasma substitutes on gelatin basis. In other cases histamine release in animals may not be relevant for man as demonstrated for dextran. Even if a small histamine release could be detected in human subjects as in the case of dextran this must not implicate that also in severe anaphylactoid incidents histamine release is the cause of these events.

Plasma histamine determinations led to a much better understanding of histamine-induced reactions in human subjects than other techniques and--which is the most important advantage--increase the possibility to differentiate between histamine-induced reactions and anaphylactoid reactions caused by other mediators. The suggestion in former time that histamine might be involved in all types of 'allergic' reactions induced a histamine philosophy. Differentiation, however, gives histamine its place at least in human pathophysiology.

56. Phagocytosis in the newborn infant: Humoral and cellular factors. M. E. Miller. J. Ped. 74: 255-259, 1969.

These studies have considered the separate functionos of polymorphonuclear leukocytes (PMN's) and plasma in phagocytosis of yeast particles and compared the activity of each in the newborn infant (2 to 4 days of age) with that in normal adults. Conditions of phagocytosis were rigidly controlled. A fixed ratio of yeast:PMN (100:1) was employed and phagocytosis was carried out at 37°C for 1/2 hour with constant rotation to favor randon PMN-yeast interaction. Results were highly reproducible. Plasma from newborn infants had considerably less opsonizing activity toward yeast than that from adults; following absorption of both groups of plasma with yeast, this difference was no longer found. In the presence of pooled plasma, PMN's from normal newborn infants took up a significantly lower average number of yeast particles; this difference was most apparent when plasma concentration in the system was 2 1/2% or less.

Despite the long-recognized importance of cellular and humoral factors in effective phagocytosis, the literature contains many studies of phagocytosis which have not adequately separated these components. This is particularly true of those studies concerning relative efficiency of phagocytosis in newborn infants. The methods employed in the studies reported here were specifically designed for separate evaluation of cellular and humoral factors. The data thus obtained revealed relative deficiencies of each in the newborn infant.

When incubated in the presence of pooled plasma, PMN's from newborn infants were shown to be less efficient phagocytes than those from adults. Production of labeled CO_2 from glucose-1-C^{14} by leukocytes is considerably less in the newborn infant than in the adult. It may be that metabolic activity in the infant's leukocytes differs from that in the adult, thereby resulting in a relative deficiency of phagocytosis by newborn leukocytes.

57. Effects of continuous positive-pressure ventilation in experimental pulmonary edema. P. C. Hopewell and J. F. Murray. J. Appl. Physiol. 40: 568-574, 1976.

We compared the effects of continuous positive-pressure ventilation (CPPV), using 10 cm H_2O positive end-expiratory pressure (PEEP), with intermittent positive-pressure ventilation (IPPV), on pulmonary extravascular water volume (PEWV) and lung function in dogs with pulmonary edema caused by elevated left atrial pressure and decreased colloid osmotic pressure. The PEWV was measured by gravimetric and double-isotope indicator dilution methods. Animals with high (22-33 mmHg), moderately elevated (12-20 mmHg), and normal (3-11 mmHg) left atrial

pressures (Pla) were studied. The PEWV by both methods was significantly increased in the high and moderate Pla groups, the former greater than the latter ($p<0.05$). There was no difference in the PEWV between animals receiving CPPV and those receiving IPPV in both the high and moderately elevated Pla groups. However, in animals with high Pla, the Pa_{O2} was significantly better maintained and the inflation pressure required to deliver a tidal volume of 12 ml/kg was significantly less with the use of CPPV than with IPPV. We conclude that in pulmonary edema associated with high Pla, PEEP does not reduce PEWV but does improve pulmonary function.

58. Bacterial shock. H. Shubin and M. H. Weil. J. Am. Med. Assoc. 235: 421-424, 1976.

Antibiotics--When culture and sensitivity studies are not yet available, gentamicin is given empirically. Except when it has been administered prior to the acute episode, or when infection due to Proteus, Salmonella, or Bacteroides from the reproductive system is suspected, gentamicin is the only antibiotic that is used. For Pseudomonas infections, carbenicillin is given in addition to gentamicin. In patients with infections due to both gram-negative and gram-positive organisms and those with respiratory strains of Bacteroides aqueous penicillin is administered.

Corticosteroids--Dexamethasone phosphate is given intravenously in an initial dose of 40 mg followed by doses of 20 mg at 4-hr intervals. As soon as clinical signs of shock subside, corticosteroid therapy is abruptly stopped.

Volume expansion--Physiological salt solution and plasma protein solution are used to expand plasma volume. When colloid osmotic pressure is less than 18 mmHg, fluid challenge is begun with 5% normal human serum albumin. Pulmonary artery and wedge pressures are measured during the fluid challenge to assess the capacity of the heart to handle the volume load.

Vasoactive drugs--If augmenting intravascular volume does not reverse perfusion failure, dopamine or isoproterenol may be given. However, neither of these agents is of proved value in increasing survival.

Respiratory support--Progressive perfusion failure is usually complicated by respiratory failure. Repeated measurements of arterial blood gases permit objective assessment of the oxygen requirement and the need for endotracheal intubation and mechanical ventilation.

Surgery--Abscesses should be promptly drained and grossly infected tissues removed.

59. Effect of tachycardia on left ventricular blood flow distribution during coronary occlusion. L. Becker. Am. J. Physiol. 230: 1072-1077, 1976.

The effect of heart rate on the amount and distribution of collateral blood flow was determined in open-chested dogs 1 h after coronary artery ligation. Flows to ischemic and nonischemic regions of left ventricle were measured with 7- to 10-μm diam radioactive microspheres during base-line conditions (118±6 beats/min) and again during atrial pacing at rates 20 and 40% above control (141±7 and 165±9 beats/min). During

pacing aortic and left atrial pressures and cardiac output did not change significantly, whereas ST segment elevation in epicardial electrograms increased markedly. In nonischemic myocardium, mean flow increased approximately in proportion to the increase in rate, but subepicardial (EPI) flow increased somewhat more than subendocardial (ENDO) flow. In ischemic myocardium, overall flow did not change significantly, but a redistribution from ENDO to EPI was seen. At the faster rate ENDO flow fell 25% ($p<0.02$), EPI flow increased slightly, and ENDO/EPI fell in 8/9 animals (mean 0.54-0.43, $p<0.01$). The ENDO/EPI maldistribution present in ischemic muscle is thus accentuated by tachycardia; this may account for part of the harmful effect of tachycardia in acute myocardial infarction and may help explain the disproportionate ENDO ischemia seen in angina pectoris.

60. Glucagon and the regulation of blood sugar. R. Levine. New Eng. J. Med. 294: 494-495, 1976.

It is concluded that glucagon is a potent diabetogenic factor in the absence of insulin but that physiologic amounts of insulin can overcome or prevent the effects of appreciably increased glucagon levels, at least in man. The reason for supposing that some species may react differently is the reflection that the original rediscovery of glucagon by DeDuve resulted from the injection of large doses of commercial insulin that contained glucagon as an impurity. The hyperglycemic action of glucagon was soon evident despite the simultaneous infusion of insulin into normal animals. Since it is highly unlikely that insulin and glucagon exert their seemingly opposing effects by acting in a plus-minus fashion on the same biochemical mechanism, it might clear the air if one did not expect metabolic effects from a ratio of the two peptides as measured in serum.

61. Diastolic properties of the left ventricle. W. Grossman and L. P. McLaurin. Ann. Intern. Med. 84: 316-326, 1976.

Left ventricular pressure and volume during diastole reflect the interaction of ventricular elastic, viscous, and inertial properties, and the completeness of myocardial relaxation. Myocardial relaxation may be impaired in the acutely ischemic ventricle, partly accounting for the abnormal diastolic pressure-volume relation in this condition. Altered elasticity of its wall can cause increased stiffness of the ventricular chamber, as in aortic stenosis, coronary heart disease, and infiltrative cardiomyopathies. In aortic stenosis, increased left ventricular stiffness results in an increase in pressure increment associated with left atrial contraction. Generation of such a high filling pressure is critical in maintaining adequate end diastolic sarcomere stretch in the left ventricle and probably accounts for the frequent deterioration of patients with aortic stenosis after development of atrial fibrillation or nodal rhythm. Many signs and symptoms of cardiac failure, previously attributed to impaired systolic performance, may be due partly to altered diastolic properties of the ventricular chambers.

62. The cellular basis of ischemia and infarction. Contribution of tissue acidosis to ischemic injury in the perfused rat heart. J. R. Williamson, S. W. Schaffer, C. Ford, and B. Safer. Circulation 53 (Suppl. 1): I-3 - I-13, 1976.

The isolated perfused working rat heart preparation has been used to study the effects of respiratory acidosis on myocardial metabolism and contractility. Hearts were perfused with 5 mM glucose and 10^{-2} U/ml of insulin in order to enhance metabolism of glucose relative to that of fatty acids. After perfusion with Krebs bicarbonate medium at pH 6.6, hearts rapidly ceased performing external work and peak left ventricular pressure fell by 75% after 5 minutes. Oxygen consumption, rate of ATP generation and overall glycolytic flux also declined rapidly. After about 2 min of perfusion, the fall of glycolytic flux showed a partial reversal, which was largely accounted for by increased lactate production, so that glucose oxidation decreased further. The reversal of glycolytic flux could be accounted for by partial release of H^+ inhibition of phosphofructokinase by increased tissue levels of adenosine 5'-diphosphate (ADP), adenosine monophosphate (AMP), and P_i and decreased levels of adenosine triphosphate (ATP) and creatine phosphate. The increased proportion of glucose uptake converted to lactate together with an increase of the tissue lactate/pyruvate ratio could be accounted for by inhibition of the malate-aspartate cycle combined with tissue hypoxia. Lactate accumulated in the tissue as a result of decreased permeability of the plasma membrane to lactate. Decreased oxygen delivery to the myocardium was caused by secondary constriction of the coronary vessels.

In further experiments, the coronary flow was regulated by an external pump which delivered fluid at a controlled rate into the aortic cannula above the coronary arteries, and the degree of tissue hypoxia was monitored by measuring changes of pyridine nucleotide reduction state by surface fluorescence techniques. The effects of acidosis uncomplicated by possible hypoxia were compared directly with those produced by ischemic hypoxia. The effects of acidosis under these conditions were similar to those described above, and to those produced by ischemia. From these and other data it is concluded that the effects of ischemia are caused by a lowering of the intracellular pH, which decreases the rate of energy production relative to the rate of energy demand. However, it is suggested that the primary cause of the decreased peak systolic pressure with either acidosis or ischemia is not a result of a defect of energy metabolism, but is due to alterations of the calcium cycle of the heart. Possible causes of irreversible heart failure after prolonged ischemia are discussed.

63. Continuous extracorporeal monitoring of animal blood using the glucose electrode. E. C. Layne, R. D. Schultz, L. J. Thomas, Jr., G. Slama, D. F. Sayler, and S. P. Bessman. Diabetes 25: 81-89, 1976.

A continuous extracorporeal monitoring system for blood glucose employing an electrochemical sensor is described. The sensor, about the size of a nickel, is rapid, is specific for glucose, generates its own power, and consists of two galvanic oxygen electrodes. Over one oxygen electrode is affixed a plastic matrix to which glucose oxidase is covalently bound; a blank matrix is over the other, which serves as a reference. Oxygen is consumed in the glucose-oxidase-containing matrix, decreasing the current from the underlying oxygen electrode. The current decrease is nonlinearly proportional to the glucose concentration.

The sensor is clamped between small blocks of plastic fitted with inlet and outlet nipples so that blood pumped from the animal passes over the two electrodes and thence to an automated chemical analysis for comparison. Blood is collected and anticoagulant added in a double-lumen catheter. Blood is withdrawn at the rate of 1 cc/hr.

Results obtained by use of the system in rabbits are reported. The capacity of the system to continuously monitor changes in blood glucose produced by repeated glucose tolerance is shown in hypo-, normo-, and hyperglycemic animals. Some properties of the system and its calibration are discussed.

64. Environmental and genetic factors affecting laboratory animals: impact on biomedical research. C. M. Lang and E. S. Vesell. Fed. Proc. 35: 1123-1132, 1976.

The chemical environment of laboratory animals constitutes an exceedingly important series of variables with respect to pharmacological investigations. This paper describes the effects on animals of three types of chemicals present in the environment of animal rooms of various laboratories. While it has long been recognized that insecticides in exceedingly small concentrations in animal rooms are potent inducers of hepatic microsomal enzyme activity, similar inducing effects of multiple other chemical contaminants of the animal room have been almost totally ignored. A partial list of some of these compounds appears in the first column of Table 1. Of particular interest in this context is the inducing potentiality of various essential oils employed in disinfectant sprays and air fresheners in animal rooms. Data for this inducing effect are shown in Table 5. Bickers et al. reported that extremely small single exposures of the skin to microscope emersion oils lead to marked induction of hepatic microsomal enzyme activity in both skin and liver.

65. Hamodynamik und myokardiale kontraktilitat im experimentellen tourniquet-shock. (Hemodynamics and myocardial contractility in experimental tourniquet-shock.) W. Stock, E. Geppert, W. Haase and W. Isselhard. Basic Res. Cardiol. 71: 133-149, 1976.

A reproducible tourniquet-shock has been produced in hind limbs of dogs by unilateral and bilateral extremity ischemia. The following parameters have been measured for analysing the function of the cardiovascular system: mean aortic pressure, heart rate, cardiac output, intraventricular pressure and left ventricular pressure. From these data the stroke volume, stroke work, total peripheral resistance and the parameters of heart contractility dP/dt_{max}, dP/dt_{max}:IP and t-dP/dt_{max} were derived.

During the ischemic period all circulatory parameters did not change in comparison to the controls. A tourniquet-shock developed upon recirculation of the ischemically stressed extremity, which was more pronounced after bilateral than after unilateral tourniquet survived an observation period of 5 hours duration, whereas 6 out of 8 dogs with bilateral tourniquet died of heart failure.

Upon release of the tourniquet, the cardiac output raised up to 140% of the normal value: the abruptly decreasing aortic pressure was fully compensated by a tachycardia from 100 to 190 beats/min. The parameters dP/dt_{max}:IP and t-dP/dt_{max} indicated a distinct increase of the left ventricular contractility in the early tourniquet-syndrome. Already after

30 minutes an increasing circulatory depression developed indicative of the decrease in aortic pressure, and end diastolic pressure. At the same time an increase of heart rate and total peripheral resistance occurred. The parameters of left ventricular contractility did not change markedly during the course of shock except for the final stage.

66. Die kontraktilitat des linken ventrikels des hundes im hamorrhagischen schock und nach volumenersatz. (Myocardial contractility in dogs in hemorrhagic shock and after volume replacement.) F. Jesch, L. Sunder-Plassmann, U. Lohrs, and K. Meßmer. Anaesthesist 25: 19-26, 1976.

Myocardial contractility was evaluated in 8 of 14 anesthetized mongrel dogs during hemorrhagic shock and after volume replacement with Dextran 60 using the force-velocity relation of the contractile elements at zero load (V_{max}). 7 animals received 50,000 or 20,000 KIE respectively of a proteinase inhibitor after bleeding and immediately before and one hour after the infusion of Dextran 60. The release of the lysosomal enzymes acid phosphatase and β-glucuronidase was inhibited significantly ($p<0.05$) in the animals treated with Trasylol. However, the inhibition of the lysosomal enzymes seems not to have a decisive influence on the dynamic of the macro- and microcirculation and the myocardial contractility.

67. Histamine (second of two parts). M. A. Beaven. New Eng. J. Med. 294: 320-325, 1976.

It is difficult to bring unity to the subject of histamine; perhaps there is none. Because it is one of the simplest of the amines to synthesize (its precursor, L-histidine, is immediately available in all tissues), it may have been adopted by nature for several purposes. The phylogenetic studies of Reite may hint at these purposes--for example, the association of histamine with the stomach early in evolution and with the mast cell in terrestrial animals later in evolution. In the higher animal, histamine is the predominant vasoactive substance in most tissues. Unlike fish, the terrestrial animal is exposed constantly to airborne particles that by their nature must contain injurious elements in a localized concentrated form. Adaptation to the land must have involved the ability for localized tissue reaction to such airborne particles, especially in lung and skin. Whatever the role of histamine, the inescapable fact is that it is present in preformed stores in sufficient quantity to flood the tissue upon release in response to specific and nonspecific stimuli. One must return to the thought that it exists as a first-line defense against injury or in immunologic reactions.

68. A practical guide to granulocyte transfusion therapy. J. A. Russell and R. L. Powles. J. Clin. Path. 29: 369-379, 1976.

A major development for the supportive care of patients with bone marrow suppression has been the recent introduction of techniques for collecting granulocytes from suitable donors. There is increasing awareness in this country that granulocyte transfusion for infected neutropenic patients is now a practical possibility, and the demand for granulocytes from those centres able to provide this service has increased considerably. It seems

therefore an appropriate time to give some account of the available methods of collecting granulocytes, the evidence for their value, and the indications for their use.

We feel that there is now enough evidence to suggest that granulocyte transfusion is a valuable procedure in certain clinical situations. However, there is still a need for controlled trials to define more precisely those situations in which this form of treatment can be used to the greatest advantage. For example, it would be useful to know if prophylactic granulocyte transfusions are needed in addition to other preventive measures during marrow transplantation, or if early treatment of certain specific infections, such as perianal cellulitis, could make enough difference to consider using them as a routine in such conditions.

The aim of any unit involved in a cytotoxic chemothrerapy programme for haematological malignancy should be to produce a situation in which very few patients with controllable malignant disease die of infection. The addition of granulocyte transfusions to a good programme of supportive care may help to achieve this aim.

69. A physiological basis for the development of opportunistic infections in man. J. W. Alexander and J. L. Meakins. Ann. Surg. 176: 273-287, 1972.

Physiologic variations in neutrophilic function occur normally in man, having a cyclic rhythmicity with a period approximating 14-24 days. Acquired abnormalities of neutrophilic antibacterial function, such as those which have been extensively documented in burn and transplant patients, are superimposed upon the physiologic abnormalities associated with the cycle causing periods when neutrophilic function, as expressed by the NBI, is extremely poor. Regardless of the basis for the defects, increasing abnormalities of neutrophil function have been significantly associated with increasing susceptibility to the development of life-threatening sepsis. The control mechanism for the periodic function has not yet been elucidated. In the acquired abnormality, however, leukocytes phagocytize normally and degranulation appears to be intact, thus implicating one or more intraleukocyte bactericidal mechanisms, notably the enzymes contained in lysosomal granules. Within neutrophils, there are a multiplicity of bactericidal mechanisms with different specificities, and bactericidal efficiency for four separate organisms were observed to vary at different times. This observation suggests that the mechanisms are extremely complex, and an abnormality of any single intraleukocyte bactericidal mechanism cannot be expected to explain the spectrum of acquired abnormalities which ahve been observed. Bacteria have been noted to multiply within burn neutrophils, associated with an arrest of the bactericidal mechanisms after one hour, to produce an intracellular infection. While inside leukocytes, the bacteria are protected from the lethal or inhibitory effects of antibiotics.

From our clinical and laboratory observations during the past five years and from the supporting evidence provided by other investigators, we advance the hypothesis that abnormalities of neutrophilic function appear to be the most important variable of immunological defense relating to the development of opportunistic infections in man.

70. Current concepts on mechanisms and treatment of cardiogenic shock. P. L. da Luz, M. H. Weil, and H. Shubin. Am. Heart J. 92: 103-113, 1976.

Cardiogenic shock following acute myocardial infarction is associated with significant reductions in stroke volume and cardiac output. These hemodynamic defects in turn account for reduced arterial pressure, increased left ventricular volume, wall tension, heart rate, and peripheral vascular resistance. Increases in wall tension, heart rate, and peripheral resistance augment myocardial oxygen demand. Coronary flow is impaired by reduction in arterial pressure and by coronary stenosis. An imbalance between oxygen supply and demand persists; consequently, myocardial ischemia is propagated and "pump failure" becomes irreversible. As cardiac output is reduced systemic oxygen availability is curtailed and progressive lactic acidosis is likely to terminate in fatal perfusion failure.

Major advances in bedside monitoring have improved not only arrhythmia detection and control but more precise understanding of the hemodynamic mechanisms accounting for power failure. Consequently, therapy may be more objectively selected and quantitated. Vasodilator agents are emerging as potentially useful alternatives for the reversal of advanced heart failure. The combination of assisted circulation and early myocardial revascularization gives promise of improving immediate survival. Whether the overall mortality rate in cardiogenic shock will be substantially decreased by such major interventions is as yet unknown.

Since the extensiveness of myocardial injury is the primary determinant of survival, current research has focused on therapeutic modalities which may reduce infarct size. Substantial experimental data are already available and well-controlled clinical trails are now warranted. Preservation of ventricular myocardium following acute infarction may be the most effective means to reduce deaths from cardiogenic shock.

71. Development of gluconeogenic enzymes in the liver of human newborns. C. Marsac, J. M. Saudubray, A. Moncion, and J. P. Leroux. Biol. Neonate 28: 317-325, 1976.

During their first hours of life, human newborns exhibit a transitory hypoglycemia which appears to be deeper and more durable in premature and 'small for gestational age' infants than in normal ones. Hepatic activities of fructose diphosphatase, pyruvate carboxylase and phosphoenolpyruvate carboxykinase (PEPCK) were measured as a function of age in premature or full-term infants: 41 postmortem samples and four biopsies from living children. All three enzymic activities were found to increase during the first 10 days of life, particularly PEPCK which may then be postulated to bear an important function in the postnatal regulation of blood sugar levels. The development of PEPCK activity begins after a lag period of 4-5 days after birth. The possible influence of prematurity and glucose infusions on the time course of PEPCK induction is discussed.

72. The critical relationship of intravascular blood volume and vascular capacitance in sepsis. A. P. Thal, R. G. Robinson, T. Nagamine, R. Pruett, and A. V. Wegst. Surg. Gynec. Obstet. 143: 17-22, 1976.

The present article represents a more detailed study of the septic leg models used in our previous work on sepsis and septic shock. An improvement in this model is described, and the period of maximum hyperdynamic response is

delineated. An attempt was made to measure changes in the rate of swelling of the septic leg in responding and nonresponding dogs.

The exquisitely sensitive response of the dog with sepsis to minor reductions in blood volume was demonstrated. Results of our previous studies concerning the redistribution of blood flow in sepsis were extended using radioactively labeled microspheres.

In humans, sepsis and septic shock often develop on a background of severe underlying disease, whereas the animal model is created in a previously healthy subject. Why some dogs respond with the hyperdynamic circulatory response and others fail to do os is still not absolutely clear. It appears also from results of studies reported herein that the responding dog with sepsis, which all our evidence suggests is in a vasodilated state, is critically sensitive to relatively small losses of blood volume.

73. Enteral hyperalimentation. M. V. Kaminski, Jr. Surg. Gynec. Obstet. 143: 12-16, 1976.

Parenteral hyperalimentation, when used free of associated morbidity, usually produces a dramatic reversal in the deteriorating clinical course of the patient. However, most patients who need nutritional support have at least a minimally functioning gastrointestinal tract.

By using a continuous enteral gavage of a chemically defined diet through a 4F tube, the same positive nitrogen balance, weight gain and accelerated wound healing can be achieved. As with parenteral hyperalimentation, there are avoidable iatrogenic morbidities. A policy and procedure for safe and effective enteral hyperalimentation, results of clinical experience and a simplified method for assessing achievement of a therapeutic goal are presented.

74. Endotoxemia associated with the Jarisch-Herxheimer reaction. J. A. Gelfand, R. J. Elin, F. W. Berry, Jr., and M. M. Frank. New Eng. J. Med. 295: 211-213, 1976.

In summary, the Jarisch-Herxheimer reaction followed penicillin therapy in two patients with secondary syphilis described in this article. The cases provide evidence that the reaction is accompanied by an endotoxemia and that complement consumption due to circulating antigen-antibody complexes does not play a major part in the pathophysiology of this reaction.

75. The role of myocardial edema in the left ventricular diastolic stiffness. G. Pogatsa, E. Dubecz, and G. Gabor. Basic Res. Cardiol. 71: 263-269, 1976.

It has been shown that simultaneous administration of norepinephrine (10 µg/kg/min) and drotaverine (200 µg/kg/min) does induce interstitial myocardial edema which tends to increase left ventricular diastolic stiffness. These results suggest that in myocardial ischaemiz temporary increase of left ventricular diastolic stiffness may be caused by interstitial edema.

76. Pulmonary capillary permeability--A transfusion lesion. I. R. Berman, H. Iliescu, J. H. C. Ranson, and K. Eng. J. Trauma 16: 471-481, 1976.

Massive transfusion of bank blood has been implicated as a major etiologic factor in the evolution of pulmonary insufficiency after injury. In spite of the demonstration of significant debris, including aggregates, in stored blood, a precise and reproducible pulmonary effect of transfusion has not previously been demonstrated. Since clinical pulmonary insufficiency is frequently accompanied by increased lung water, these experiments were designed to measure pulmonary capillary permeability and its response to transfusion of blood and blood components in rats.

These experiments demonstrate that: (1) the rat lung is a target organ with regard to blood transfusion; (2) the lung lesion with transfusion is attributable, at least in part, to a selective and acute increase in pulmonary capillary permeability; (3) pulmonary capillary permeability is highly responsive to viable platelets; (4) prolonged storage of blood in polyvinyl chloride containers may enhance its ability to induce pulmonary capillary permeability; (5) increased capillary permeability with transfusion is largely eliminated when platelets and buffy coat are eliminated.

77. Role of platelets in the pathogenesis of canine endotoxin shock. A. H. L. From, J. S. C. Fong, T. Chiu, and R. A. Good. Infect. Immun. 13: 1591-1594, 1976.

Endotoxin-platelet interactions are thought to be of major importance in the response of dogs and other species to bacterial endotoxin; the mechanisms postulated are: (1) the release of vasoactive substances, (2) the formation of occlusive platelet aggregates, and (3) induction of intravascular coagulation. The role of platelets in canine endotoxin shock was examined in animals with thrombocytopenia induced by estrogen pretreatment ($\leq$10,000 platelets/mm^3) and in controls. After intravenously administered endotoxin, the hemodynamic responses, mortality, and gross necropsy findings were similar in both groups. These data indicate that endotoxin-platelet interactions are not determinative in the pathogenesis of canine endotoxin shock.

78. Cerebral and hepatic blood flow measured during shock using the mass spectrometer. F. J. Gerratana, H. J. Saranchak, and G. Owens. J. Surg. Res. 20: 489-492, 1976.

This study verifies that the brain is the critical organ whose perfusion is preserved during hypovolemia, while the hepatic circulation is significantly compromised. The shock model maintained a mean arterial pressure of 35 mmHg during which time cerebral blood flow decreased by one-third with no reduction of cerebral oxygenation. However, liver perfusion, with less of a tolerance for hypotension, demonstrated a two-thirds reduction in flow creating a 51% decrease in oxygenation. Giving isoproterenol during this hypotensive period was of no value in improving perfusion or oxygenation in either the brain or liver.

79. Effects of allopurinol, propranolol and methylprednisolone on infarct size in experimental myocardial infarction. C. H. Shatney, D. J. Maccarter, and R. C. Lillehei. Am. J. Cardiol. 37: 572-580, 1976.

With use of a canine model of occlusion of the left anterior descending coronary artery and an intracellular lactic dehydrogenase stain to measure infarct size

directly, the effects of allopurinol, methylprednisolone sodium succinate and propranolol were studied. Allopurinol did not influence the extent of myocardial necrosis, whereas both methylprednisolone and propranolol significantly reduced myocardial infarct size. Possible mechanisms of action and clinical applicability of these agents are discussed.

Methylprednisolone sodium succinate, administered as an intravenous bolus injection of 30 mg/kg, significantly reduced myocardial infarct size. Hemodynamically, administration of methylprednisolone was associated with an increase in mean intra-arterial blood pressure, an insignificant increase in cardiac index and a decrease in total peripheral resistance index. The average coronary sinus lactate concentration was greater than that in untreated animals but, as in propranolol-treated dogs, the lactate pattern suggested a "washout" of lactate from previously underperfused myocardium. The reasons for the efficacy of corticosteroids in low flow states remain obscure. Myocardial ischemia is associated with abnormal structural and functional changes in intracellular organelles, especially the lysosome and mitochondrion, and methylprednisolone sodium succinate exerts membrane-stabilizing effects in cardiac cells similar to those demonstrated in the lung, liver and kidney. In addition, the administration of a pharmacologic dose of this corticosteroid causes an elevation of the blood glucose concentration and thus increases the amount of substrate potentially available for myocardial metabolism.

In sum, the protective influence of methylprednisolone sodium succinate on ischemic cardiac tissue is probably due to beneficial effects on both coronary hemodynamics and myocardial cellular structure and metabolism. The dose used in this investigation, 30 mg/kg, is identical to that used and well tolerated in patients with cardiogenic shock. Hence, clinical studies are now underway to examine the effects of methylprednisolone sodium succinate in patients during cardiopulmonary bypass and after acute myocardial infarction.

80. Metabolic consequences of glucose-insulin-potassium infusion in treatment of acute myocardial infarction. J. W. Prather, R. O. Russell, Jr., J. A. Mantle, H. G. McDaniel, and C. E. Rackley. Am. J. Cardiol. 38: 95-99, 1976.

Eighteen patients treated with glucose-insulin-potassium infusion for anaerobic support of acutely ischemic myocardial tissue were studied to ascertain the metabolic consequences of this therapy for acute myocardial infarction. Twelve patients with acute myocardial infarction were treated in a conventional manner and served as control subjects. The glucose-insulin-potassium solution was composed of 300 g of glucose, 50 units of regular insulin and 80 mEq of potassium ion per liter, and was infused at a rate of 1.5 mg/kg per hour through the right atrial port of an indwelling Swan-Ganz thermodilution catheter. Serial measurements of serum electrolytes, cardiac and hepatic enzymes, glucose and osmolality were obtained every 4 to 6 hours for 4 days. Twenty-four hour urinary volume and potassium levels were measured daily. Pulmonary arterial end-diastolic pressure was measured hourly and the cardiac index daily for the duration of the study. Serum potassium increased to 5 mEq/liter during the infusion and to more than 6 mEq/liter after infusion in 28% of patients. No recognizable complications or arrhythmias accompanied this transient hyperkalemia. Potassium balance studies revealed a net total body potassium ion gain of 120 mEq during the study. The second most frequent finding was an elevation of serum glucose (mean 175 mg/100 ml); in all instances this was controlled with supplemental administration of insulin. The serum osmolality and fluid balance remained normal in all patients during the study. Serum glutamic oxaloacetic transaminase (SGOT) and fraction 5 of lactic dehydrogenase (LDH) were increased in 34%

of the patients during the last 12 to 18 hours of the glucose-insulin-potassium infusion. Characterization of these enzymes suggested a hepatic origin for these changes. This study suggests that glucose-insulin-potassium infusion is a relatively safe procedure in which postinfusion hyperkalemia is the most serious potential complication.

81. The mechanism of phagocytosis. T. P. Stossel. J. Ret. Soc. 19: 237-245, 1976.

Phagocytosis, the first useful function ascribed to macrophages, is among the least understood. Direct scrutiny with the light microscope of cells ingesting particulate objects (particles) reveals to the observer what must be understood to explain phagocytosis. Phagocytosis can be divided, like life, into 7 morphologic events: 1) certain particle surfaces but not others elicit recognition by the phagocyte; 2) the phagocyte receives the message of recognition; 3) the phagocyte transmits this message to its cytoplasm, arousing effector mechanisms which 4) cause the plasma membrane to adhere strongly to the particle; 5) induce pseudopods to assemble and 6) move around the particle and 7) make the tips of the pseudopods fuse at the distal side of the particle. One or more of these events (recognition, reception, transmission, adhesion, pseudopod assembly, pseudopod motion and pseudopod fusion) are energy-dependent. The morphology of phagocytosis is essentially the same for all cells, a helpful fact often overlooked. The discussion of this paper is a brief prejudiced review of recent work concerning the mechanism of phagocytosis.

An understanding of the mechanism of phagocytosis is slowly advancing. This progress is good, because the significance of phagocytosis is greater than the mere alimentation of a scavenger cell. It encompasses the mechanisms of cellular recognition, cell surface to cytoplasm communication, cell movement and membrane fusion, all events of broad biologic importance.

82. Oxygen metabolism in the alveolar macrophage: Friend and foe? J. B. L. Gee and A. S. Khandwala. J. Ret. Soc. 19: 229-236, 1976.

The pulmonary alveolar macrophage (AM) became an important subject for study when Myrvik's laboratory first developed the simple technique of pulmonary lavage to obtain them in a nearly pure single cell line. This account will review and speculate on certain aspects of O_2 metabolism in the AM. It will also include a few studies illustrating some mechanisms of impaired phagocytosis by the AM. Further details and more extensive references are found in other reviews.

This brief review has emphasized the role of O_2 as an energy source for phagocytosis and as a source of antimicrobial agents. These O_2 reductions at 2 sites, the mitochondrion and phagosome, serve 2 distinct functions. In addition, localized intravacuolar O_2 reduction is important in host defense, but unregulated and illocalized O_2 reduction is potentially host destructive. Detailed information on regulation and localization may, therefore, be important in future studies.

83. Role of ischemia in the induction of changes in cell membrane during hemorrhagic shock. A. Arango, H. Illner, and G. T. Shires. J. Surg. Res. 20: 473-476, 1976.

Sustained hemorrhagic shock results in consistent depression of the transmembrane potential difference in the skeletal muscle cell. Ischemia produces abrupt changes in the skeletal muscle membrane potential (PD) after a variable

but long period of electrogenic normality. In the presence of shock, a tourniquet isolated extremity would show the changes of ischemia, but not those of shock. The PD changes seen during hemorrhagic shock appear not primarily related to tissue ischemia.

84. Metabolic effects of β-adrenoreceptor blockers. H. J. Waal-Manning. Drugs 11 (Suppl. 1): 121-126, 1976.

The effects of β-blockade on glucose metabolism are complex. Some patients with impaired glucose tolerance while taking a non-selective β-blocker, showed some improvement in glucose tolerance when therapy was changed to a β-blocker (metoprolol). Serum K^+ values tend to rise slightly on β-blocking therapy; small increases in serum urea and creatinine also occur. A rise in plasma triglycerides was noted in patients starting β-blocking therapy; this effect seemed to be more marked on metoprolol than on non-selective β-blockers.

85. Leukocyte colony-stimulating factor and inhibitor activity. R. K. Shadduck. J. Lab. Clin. Med. 87: 1041-1049, 1976.

Native and density gradient separated rat peritoneal exudate cells were evaluated for both their capacity to stimulate granulocyte colony formation and their ability to inhibit colony growth in vitro. Granulocyte colony-stimulating factor (CSF) was primarily elaborated by monocytes and macrophages; neutrophils showed only minimal stimulatory activity. In contrast, freeze-thawed extracts of both monocyte-macrophage and granulocyte fractions were markedly inhibitory to colony growth using a standard L-cell-derived CSF. Characterization of the inhibitory material indicated it to be a low molecular weight, nonlipid, heat-stable substance. In addition to peritoneal leukocytes, other tissues including lymph node, thymic and splenic lymphocytes, liver, kidney, and skeletal muscle also contained inhibitory materials. These observations suggested that granulopoiesis, as assessed by in vitro culture techniques, is not influenced solely by a simple feedback loop; rather, leukocytic elements, as well as other tissues, appear to contain and release both stimulatory and inhibitory factors.

86. Portal and peripheral vein insulin responses to intravenous glucose in the rhesus monkey. E. J. Rayfield, R. T. Faulkner, and W. Cazjkowski. J. Lab. Clin. Med. 87: 919-924, 1976.

Catheterization of the portal vein and bilateral femoral veins were performed under general anesthesia in 6 healthy male rhesus monkeys. Four days later, sequential, simultaneous peripheral and portal plasma samples were obtained for glucose and immunoreactive insulin determinations before and after administration of 0.5 Gm of glucose per kilogram (over a 1-minute period) via the opposite peripheral catheter. Two phases of insulin secretion were noted in both portal and peripheral plasma samples. An immediate early-phase insulin response was noted with a peak response at 1 minute followed by a rapid decline to a nadir at 5 minutes. A second phase of insulin secretion was evident with a peak response at 10 minutes and a subsequent decline to basal levels by 60 minutes. Simultaneous portal vein and peripheral vein glucose concentrations were not significantly different from each other by paired analysis. Thus, in the rhesus monkey peripheral insulin concentrations following intravenous glucose exhibit a biphasic response closely paralleling pancreatic insulin secretion.

87. Commentary. The kinins. (A status report.) E. G. Erdos. Biochem. Pharmacol. 25: 1563-1569, 1976.

Although kallikrein was discovered half a century ago, recent years have seen involvement of the kallikrein-kinin system in other areas of research, so much so that it is increasingly difficult for many to put this system into perspective. The purpose of this commentary is to give an overview of the field as related to other research areas.

This brief survey of the literature indicates that the components of the kallikrein-kinin-kininase systems have functions other than the release and inactivation of kinins. They contribute to blood clotting, to the inactivation of anaphylatoxins, to the activation of plasminogen and angiotensin I, etc. Kinins themselves are hypotensive; they increase capillary permeability, cause pain and are chematactic to leucocytes, but in addition they release other agents such as cathecholamines, histamine or prostaglandins and can accentuate or modify the primary actions of the agents.

88. Leukotactic responses. P. A. Ward. J. Ret. Soc. 19: 247-248, 1976.

Leukotactic responses are currently measured most commonly by the use of micropore filters in modified Boyden chambers. Quantitative problems in assessing migration of leukocytes have been diminished by the use of radio-tagged leukocytes which are trapped in the interstices of a second filter. Another modification of quantitative approaches is the "leading front" technique in which the depth of penetration of migrating cells is the parameter measured. Neither of these 2 modifications has yet replaced the conventional morphologic approach. The structural basis of chemotactic activity is under considerable study. There are some suggestions that tertiary structural changes in peptides or proteins, resulting in the exposure of hydrophobic regions, account for the acquisition of chemotactic activity. However, on the basis of studies with synthetic peptides, there is firm chemical evidence that the primary structure is a critical factor in chemotactically active compounds.

Several biochemical parameters reflect interaction of a chemotactic factor with the leukocyte: increased oxygen uptake by the cell, glycolysis, activation of the hexose monophosphate shunt and activation of a proesterase. Additional concomitant changes include lysosomal enzyme discharge and assembly of microtubles.

The sources of leukotactic factors include plasma proteins and cells. The former category includes the complement proteins (related to the third, C3, and the fifth, C5 components), kallikrein and the plasminogen activator. The latter category includes, by and large, cell-released enzymes that can cleave C3 or C5, and newly formed products released after cell or tissue activation following contact with antigen. The products released from cells consist of the preformed eosinophil chemotactic factor and newly synthesized proteins. such as the monocyte chemotactic factor released from stimulated lymphoid cells.

Regulation of the leukotactic system occurs by the action of 2 different inhibitors found in human serum: the chemotactic factor inactivator (CFI) and the cell directed inhibitor (CDI). Chemotactic factor inactivator reacts irreversibly with leukotactic factors, is present in low concentrations in human serum and exists in 2 forms in serum: an α globulin which has specificity for the C5 fragment and a β globulin which interacts specifically with the C3 leukotactic fragment. In addition to reactivity with leukotactic factors, CFI

also inactivates the migration inhibitory factor produced by lymphoid cells. Current studies indicate that CFI has the enzymatic activity of an amino peptidase. Cell directed inhibitor is cell directed in its action and blocks the ability of both neutrophils and monocytes to respond to a variety of leukotactic stimuli. Cell directed inhibitor also impairs the phagocytic responses of neutrophils. When plasma/serum levels of either CFI or CDI are elevated, there are evidences of impairment of the inflammatory response.

89. Myocardial depressant factor and steroid therapy in cardiogenic shock. (Questions and Answers section of J.A.M.A. 235: 2433-2434, 1976.)

Question: According to recent reports, glucocorticoids in large doses are of value early in cardiogenic shock because they decrease the circulating myocardial depressant factor (MDF), a substance with toxic effects that lessen chances of survival. Please have your consultant comment on this concept and also on the role of MDF in the pathogenesis of shock.

This question was referred to several consultants, whose discussions are as follows:

Many laboratories around the world have confirmed the presence of a myocardial depressant factor (MDF) in the plasma of animals and patients in a variety of types of circulatory shock (Mod. Con. Cardiovasc. Dis. 42:59, 1973; Klin. Wochenschr. 52:325, 1974). A few laboratories do not find MDF in the plasma as a result of technical errors in procedure. Myocardial depressant factor is a small peptide having a molecular weight of about 500. Recently, MDF has been isolated and found to contain four to five amino acid residues. Work is in progress on the amino acid sequence of this small peptide.

Myocardial depressant factor is produced by the ischemic pancreas during hemorrhagic, septic, cardiogenic, bowel ischemic, burn, and acute pancreatic shock. The principal stimuli for its formation are ischemia and hypoxia, which trigger lysosomal disruption and zymogenic activation of proteases within the pancreas; MDF is then formed by the massive autolytic proteolysis within the pancreas.

Myocardial depressant factor is a potent substance exerting a profound negative inotropic effect on cardiac contractility. In addition, it constricts the splanchnic vasculature (which enhances its formation) and depresses components of the reticuloendothelial system (which impairs its clearance from the circulation) Thus, MDF exerts toxic effects that compromise survival in shock. The best way to prevent MDF formation is early administration of massive doses of glucocorticoids such as methylprednisolone or dexamethasone.

Early administration of glucocorticoids (i.e., methylprednisolone, 30 mg/kg or dexamethasone, 6 mg/kg) is very useful in the treatment of a variety of types of circulatory shock as well as in the early stages of acute myocardial ischemia. The major mechanism for this protective effect appears to be stabilization of cell membranes, including lysosomal and plasma membranes. This membrane-stabilizing effect has the dual action of preventing the release of hydrolytic enzymes from lysosomes and preventing the loss of intracellular contents. Therefore, in the pancreas these agents prevent the release of lysosomal proteases and thereby the action of the proteases on cellular proteins, thus preventing the formation of MDF. In the heart, glucocorticoids prevent autolytic myocardial cellular damage, thereby preventing the spread of the infarcted region. This latter effect has recently been confirmed in patients with acute myocardial infarction (Crit. Care Med. 3:94, 1975).

A. M. Lefer

Since the turn of the century, toxic factors have been implicated in circulatory shock, including cardiogenic shock, but to date none have had sustained importance as primary factors in the pathogenesis of shock. Over the past few years, a hypothesis has been developed, primarily by Allan Lefer, PhD, that during circulatory shock a myocardial depressant factor (MDF) is produced that depresses myocardial performance and hastens death. Reported to be a small peptide with a molecular weight of 500 to 1,000, MDF is presumably produced within the ischemic panreas.

Using the cat papillary muscle assay system as described by Lefer, we have examined unprocessed plasma, ultrafiltered plasma, dialyzed plasma, column-eluted fractions of plasma, and desalted ultrafiltrates of plasma for MDF activity. Our subjects were shocked animals and patients in a variety of shock states, including cardiogenic shock after myocardial infarction. We have also employed high-voltage electrophoresis, several systems of thin-layer chromatography, and techniques of sequential amino acid analysis in the search for a peptide. We have found no evidence for a peptide with myocardial depressant activity. In all cases, myocardial depressant activity could only be correlated with changes in sodium concentration and, to a lesser degree, calcium concentration, and thus represented an artifact of the bioassay system (J. Trauma 13:181, 747, 1973). More recently, Barenholz et al. reported a paper chromatographic assay for MDF in which a ninhydrin staining band termed "G" represented MDF. We have reproduced the chromatogrpahic assay and have identified band "G" as the amino acid alanine, which is known to be markedly elevated in the plasma in shock states, but has no myocardial depressant activity.

There are only a few laboratory groups who have found MDF activity in plasma, ultrafiltrates, or column-eluted fractions of plasma with the cat papillary muscle assay. We would urge that investigators carefully study their assay techniques to be certain the the depressant activity is truly due to a peptide and not to changes in sodium or calcium conentrations or other artifacts.

We belive it is fair to say that the MDF hypothesis is controversial. E. D. Brand, Ph.D., who was the primary author of the first publication regarding MDF, more recently has been unable to find MDF activity and evidence for a peptide when his assay techniques were carefully controlled. E. H. Sonnenblick, MD, found papillary muscle depression only if plasma ultrafiltrates were frozen prior to assay. Wilson and Ebert found no correlation between myocardial depressant activity and the hemodynamic state of dogs subjected to superior mesenteric artery occlusion. Using both isolated hearts and isolated papillary muscle preparations, Wilson, Gay, and Ebert concluded that there was no evidence for a specific myocardial depressant factor in dogs subjected to as long as 26 hours of oligemic shock. Furthermore, Hinshaw et al. reported no evidence for detrimental myocardial action of blood-borne substances in splanchnic arterial occlusion shock or in pancreatectomized animals receiving endotoxin. One must conclude that we do not stand alone in our inability to find a specific role in circulatory shock.

This issue of whether or not glucocorticoids in large doses are of value in cardiogenic shock after myocardial infarction in patients remains unsettled at this time. There is increasing evidence accumulating from animal experiments that large doses of steroids may alter acute ischemic injury of the myocardium and subsequent necrosis, thereby limiting infarct size following coronary occlusion. Presumably, protection afforded by steroids is related to cellular

membrane stabilization and prevention of autolytic and heterolytic processes caused by lysosomal enzyme release. However, clear evidence of improved survival with steroid therapy in human patients in cardiogenic shock after myocardial infarction is not available.

S. L. Wangensteen, R. S. Crampton, and W. W. Ferguson.

90. Coronary perfusion and myocardial metabolism during open-heart surgery in man. B. G. Barratt-Boyes, E. A. Harris, A. M. Kenyon, C. A. Lindop, and E. R. Seelye. J. Thor. Cardiovasc. Surg. 72: 133-141, 1976.

There is as yet no consensus about the conditions of artificial coronary perfusion necessary to provide optimal survival of the myocardium during open-heart surgery. In particular, the optimal coronary perfusion pressure and flow during aortic valve replacement in hearts with left ventricular hypertrophy are conjectural. In this report the effects of altering coronary pressure and flow on myocardial metabolism are examined in six patients during this operation.

Myocardial oxygen consumption and extraction of lactate and free fatty acids (FFA) have been measured in six patients during cardiopulmonary bypass at two coronary flow rates differing by 25% (109 and 148 ml/min). Significant differences were found between these flows and between natural and artificial coronary perfusion. This fact indicates the presence of anaerobic metabolism, especially at the lower coronary flow. These findings are discussed in relation to criteria for coronary flow and perfusion pressure during open-heart procedures.

91. Myocardial utilization of hypertonic glucose during hemorrhagic shock. J. F. Stremple, H. Thomas, V. Sakach, and D. Trelka. Surgery 80: 4-13, 1976.

Glucose has been given to provide added energy substrate in hemorrhagic and endotoxin shock and cardiopulmonary bypass. Awake pigs were rapidly bled 40% of total blood volume to induce hemorrhagic shock. Immediately after the induction of shock, all pigs received a single intravenous injection of radioactive-labeled glucose-U-^{14}C. Simultaneously with glucose-U-^{14}C injection, 10 pigs received single central intravenous injections of unlabeled 50% glucose, 4 pigs received equiosmolar 25% mannitol, 6 did not receive either 50% glucose or mannitol, and 2 received 50% glucose plus insulin. Mean arterial pressure with 50% glucose was 89.9 mmHg at 15 minutes of shock and significantly higher than without 50% glucose, 48.3 mmHg or after mannitol, 46.7 mmHg($p=0.05$). Mean cardiac output at 10 minutes of shock with 50% glucose was 2.24 L/min and significantly higher than with mannitol, 1.34 L/min, or without 50% glucose, 0.94 L/min ($p=0.05$). Evidence for increased anaerobic myocardial utilization of the administered unlabeled 50% glucose was shown by a 12% greater production of unlableed lactate in the venous coronary sinus blood from unlabeled 50% glucose in contrast to those not given 50% glucose at 10 minutes after shock ($p=0.05$). Also, 50% glucose significantly increased mean arterial pressure, cardiac output, and survival over both control groups.

92. Effect of nitroprusside in local contractile performance after coronary ligation and reperfusion. V. S. Banka, M. M. Bodenheimer, and R. H. Helfant. Am. J. Cardiol. 37: 544-549, 1976.

Recent studies have shown that nitroglycerin and nitroprusside improve overall left ventricular function in patients with acute myocardial infarction. However, the effect of such agents on regional contractile function of the left ventricle is unknown. To study the effects of nitroprusside infusion on the regional contractile performance of the left ventricle after coronary occlusion,

local tension and segment length of the ischemic, border and nonischemic zones were studied using Walton-Brodie strain gauge arches and mercury-in-Silastic tubing segment length gauges in open chest dogs. The effect of this intervention on the time period for functional reversibility of the affected areas after revascularization was also examined. Fifteen minutes after occlusion of the left anterior descending coronary artery, nitroprusside (4-11 μg/kg/min) was infused to keep systolic pressure 20-25% below control levels for 2 hr after occlusion and then 1 hr after reperfusion. The ischemic zone showed no change in either tension or length although there was a gradual continuing decrease in tension. However, in the border zone, total tension, which had decreased to 81.4±9.6 (standard error of the mean) % of control level 15 min after coronary occlusion, increased to 87.5±11.3 % immediately after nitroprusside infusion and continued at that level for 2 hr. Preejection tension, rate of tension rise and ejection tension demonstrated parallel increases. Segment length, which had increased to 144.1±4.5 % of control level after coronary occlusion, declined to 115±10.7 % ($p<0.02$) immediately after the onset of infusion. The nonischemic zone showed a sustained increase in all tension variables ($p<0.01$) and a decrease in segment length during the period of nitroprusside infusion with a return to control value after discontinuation of the infusion. The immediate deterioration in tension in the ischemic zone caused by reperfusion after 2 hr of occlusion was prevented by nitroprusside. The border zone continued to maintain improved tension after reperfusion but exhibited an immediate decrease from 84.1±7.8 % to 69.1±11.7 % ($p<0.05$) after discontinuation of nitroprusside.

In summary, nitroprusside infusion provides a sustained increase in tension and decrease in length of the border and the nonischemic zones after acute coronary occlusion whereas the ischemic zone remains unaffected. Although administration of nitroprusside fails to prolong the time period for functional reversibility of the affected zones with reperfusion, it appears to prevent further deterioration.

93. Methylprednisolone treatment in acute myocardial infarction. Effect on regional and global myocardial function. J. Osher, T.-W. Lang, S. Meerbaum, K. Hashimoto, J.-C. Farcot, and E. Corday. Am. J. Cardiol. 37: 564-571, 1976.

Corticosteroid therapy, which has been advocated for the treatment of the serious complications of myocardial infarction such as cardiogenic shock and heart block, has recently been proposed as a form of therapy to reduce infarct size. The ability of corticosteroids to salvage acutely ischemic myocardium was inferred from observations that their administration reduced epicardial S-T segment elevations and improved tissue creatine phosphokinase (CPK) levels as well as histologic appearance 24 hours after acute coronary occlusion. Recently, administration of methylprednisolone in patients with acute myocardial infarction was reported to reduce infarct size as judged from sequential serum CPK determinations. However, debate continues on whether corticosteroids can correct the regional cardiac dysfunction in acute ischemia and eventually save the jeopardized myocardium.

The effects of methylprednisolone treatment on acute myocardial ischemia were studied in 9 closed chest dogs. After 1 hr of proximal occlusion of the left anterior descending coronary artery, an intravenous bolus injection (50 mg/kg body wt) of methylprednisolone was administered and its effects studied during an additional 2 hrs of occlusion. After 2 hrs of treatment the following significant mean alterations from levels after 1 hr of occlusion were noted: an increase of 16.7 % in heart rate and decreases of 23% in left ventricular

end-diastolic pressure, 32% in stroke volume, 14% in cardiac output and 37% in stroke work. Peak systolic pressure, maximal rate of rise of left ventricular pressure (dP/dt), left ventricular end-diastolic volume, systemic vascular resistance and coronary sinus blood flow changed less than 10%. Ejection fraction and regional cardiac wall motion were not improved. Metabolic dysfunction of the coronary-occluded myocardium, revealed by regional lactate as well as potassium derangements, persisted throughout the 2 hr treatment period.

Comparison of these results with equivalent data from an untreated series of 9 dogs with 3 hours of occlusion demonstrated no improvement in the treated series. Methylprednisolone failed to restore regional cardiac metabolic and mechanical function, and treatment was associated with a further rise in S-T segment elevations. Administration of methylprednisolone after 1 hr of proximal left anterior descending coronary occlusion apparently does not reverse cardiac dysfunction in the first 2 hr of treatment.

94. Influence of vasodilators upon function and metabolism of ischemic myocardium. P. L. da Luz, and J. S. Forrester. Am. J. Cardiol. 37: 581-587, 1976.

Two major goals of therapy of cardiac failure after acute myocardial infarction are to augment "pump" function of the heart and to reduce the extent of ischemic injury. On the basis of hemodynamic effects, several clinical investigators have hypothesized that peripheral vasodilators might accomplish both goals. However, the effects of vasodilators upon the function and metabolism of ischemic myocardium are too complex to be inferred accurately from changes in systemic hemodynamics.

Although the systemic hemodynamic effects of vasodilators such as nitroprusside, phentolamine and nitrates are well known, relatively little information is available regarding their effects upon the function and metabolism of ischemic myocardium. Experimental and clinical studies indicate that vasodilators improve the mechanical performance of regional ischemic myocardium, probably by simultaneous reduction of peripheral resistance and reduction of the degree of ischemia. The majority of evidence, although still controversial, seems to indicate that myocardial perfusion can also be increased, particularly when coronary collateral vessels are present.

Concomitant reduction in preload contributes to reduced oxygen demand, as evidenced by findings of reduced oxygen extraction. Thus, the balance of the oxygen supply and demand may be improved as indicated by decreases in lactate production. In addition, limited evidence in experimental animals and man suggests that vasodilators may also reduce the extent of myocardial injury as measured by S-T segment mapping and the creatine phosphokinase (CPK) release technique. However, these effects are contingent upon the arterial pressure response, and directionally opposite results may be anticipated if hypotension occurs. Since the mechanism of action of vasodilators is reasonably well understood, vasodilator therapy can be administered safely in anticipation of both improvement in total cardiac performance and a decrease in severity of ischemia.

95. Beneficial metabolic effects of methylprednisolone sodium succinate in acute myocardial ischemia. T. N. Masters, N. B. Harbold, Jr., D. G. Hall, R. D. Jackson, D. C. Mullen, H. K. Daugherty, and F. Robicsek. Am. J. Cardiol. 37: 557-563, 1976.

Corticosteroids have been used successfully for several years to treat various types of shock including, recently, cardiogenic shock. The metabolic and

hemodynamic effects of methylprednisolone sodium succinate (40 mg/kg body wt) after acute myocardial ischemia were determined in 24 heparinized mongrel dogs. Myocardial ischemia was produced by ligation of the left anterior descending coronary artery. Catheters in the coronary sinus and the vein draining the left anterior descending coronary arterial area were used to collect blood samples from nonischemic and ischemic myocardium. Lactate, pyruvate, glucose, free fatty acids and oxygen were measured in arterial and venous blood from ischemic and nonischemic areas before and 3, 30 and 60 min after myocardial ischemia in animals with (Group II) and without (Group I) steroid treatment. In both Groups I and II glucose, lactate, free fatty acids, oxygen and coronary blood flow in nonischemic areas were not significantly changed, whereas glucose uptake in ischemic areas was significantly increased with myocardial ischemia and remained elevated. In Group I lactate uptake in ischemic areas became negative after coronary arterial ligation and remained so; in Group II, it increased after 30 (70%) and 60 (111%) min. Free fatty acid uptake in ischemic areas was reduced after myocardial ischemia in Group I, but in Group II it increased after 30 (224%) and 60 min (173%), and there was a concomitant increase in oxygen uptake. Pyruvate uptake in nonishcemic areas decreased after 60 min in Group I, whereas it was reduced after 30 (68%) and 60 min (513%) in Group II. The changes were similar in ischemic myocardium. There were no significant changes in hemodynamic indexes. Coronary blood flow in ischemic areas decreased in Group I after myocardial ischemia and further after 30 and 60 min, but in Group II it increased after 30 (82%) and 60 (53%) min.

The data indicate that administration of methylprednisolone results in improved collateral blood flow into the infarcted area and a significantly improved metabolic response of ischemic myocardium. The glucocorticoid may also have a direct beneficial effect on carbohydrate metabolism and cause the increased pyruvate neccessary to maintain the generation of energy-producing substrates. The results also suggest that methylprednisolone increases cell survival time and results in greater salvage of ischemic myocardium.

96. Decreased neutrophil bactericidal activity in acute leukemia of childhood. J. R. Humbert, J. J. Hutter, Jr., C. H. Thoren, and P. A. DeArmey. Cancer 37: 2194-2200, 1976.

Neutrophil (PMN) bactericidal activity, phagocytosis, and nitroblue tetrazolium (NBT) reduction were evaluted in 18 children with untreated or relapsing acute leukemia and 20 children in hematologic remission. Half of the patients in relapse demonstrated abnormal PMN bactericidal activity, while remission patients had essentially normal PMN bactericidal activity. Phagocytosis of Staphylococcus aureus was normal in relapse and remission subjects. NBT reduction by PMN's of leukemic patients was significantly lower than that of controls, but there was no correlation between decreased NBT-reductase activity and decreased bactericidal power. Six patients in remission had received intensive chemotherapy for more than 4 years, and all demonstrated normal PMN functions. Among relapse patients with abnormal PMN bactericidal activity 63% eventually developed severe bacterial infections. By comparison 20 % of the relapse patients with normal PMN bactericidal activity subsequently developed severe infections. The PMN dysfunction observed in relapse patients suggests that abnormal PMN bactericidal activity may contribute the increased susceptibility to bacterial infections during leukemic relapse.

97. Effects of coronary perfusion during myocardial hypoxia. Comparison of metabolic and hemodynamic events with global ischemia and hypoxemia. A. J. Liedtke, H. C. Hughes, and J. R. Neely. J. Thor. Cardiovasc. Surg. 71: 726-735, 1976.

The effects of metabolic accumulation on myocardial metabolism during global heart oxygen deprivation were evaluated in a working in situ swine heart preparation with controlled total coronary blood flow. Myocardial oxygen consumption was depressed to a similar extent by either reducing total coronary flow 60% (ischemia, low coronary perfusion) in 10 swine or by decreasing coronary perfusate pO_2 to 30 mmHg at normal coronary flows (hypoxemia, high coronary perfusion) in 13 swine. Compared with findings in 13 control hearts, ischemia significantly ($p<0.05$) decreased myocardial oxygen consumption (640 to 390 µmole/hr/gm), glucose uptake (185 to 16 µmole/hr/gm), and free fatty acid consumption (32 to 17 µmole/hr/gm). Tissue levels of glycogen, creatine phosphate, and adenosine triphosphate (ATP) were significantly reduced ($p<0.005$), and tissue lactate, adenosine diphosphate (ADP), and adenosine monophosphate (AMP) were increased ($p<0.001$). During hypoxemia, glucose uptake was increased (240 µmole/hr/gm) and free fatty acid consumption was somewhat less depressed (19 µmole/hr/gm). Creatine phosphate and ATP were higher than with ischemia ($p<0.001$), and lactate, ADP, and AMP accumulations were less ($p<0.01$). Thus, in the period immediately following myocardial oxygen deprivation, inadequate coronary perfusion caused greater metabolic buildup which inhibited myocardial substrate utilization and energy production. High coronary perfusion, even though the perfusate was unoxygenated, was associated with greater preservation of substrate utilization, higher levels of high-energy phosphates, less accumulation of metabolic products, and a longer survival. These data suggest a critical role of coronary perfusion in protecting myocardial metabolism in the immediate period following global heart hypoxia.

98. The protective effect of glucose-insulin-potassium on the response to atrial pacing. M. A. Chiong, R. West, and J. O. Parker. Circulation 54: 37-46, 1976.

In 1962 Sodi-Pallares reported that the administration of glucose-insulin-potassium (GIK) was beneficial in the treatment of cardiac arrhythmias in the acute phase of myocardial infarction. This has become a highly controversial issue and reports both in favor and against this therapy have subsequently appeared in the literature. More recently, GIK has been found to decrease infarct size after coronary artery occlusion in dogs, but it has also been reported to be ineffective in increasing tolerance to pacing-induced myocardial ischemia. The objective of this preliminary study was to assess the influence of GIK on the pacing-induced myocardial ischemic syndrome which consists of chest pain, ST depression and abnormalities in left ventricular end-diastolic pressure and myocardial lactate extraction.

The effects of glucose-insulin-potassium infusion (GIK) on atrial pacing-induced angina, ST depression, abnormal left ventricular end-diastolic pressure during pacing interruption (LVEDPi) and lactate metabolism (L), were studied in 18 patients: 10 had angina during pacing = Ischemic group, and 8 (5 normals and 3 with coronary artery disease) remained asymptomatic = Nonischemic group. The study consisted of 8-10 min periods of control, pacing and recovery, before and after GIK. No untoward effects were observed. Comparison of the pacing responses (GIK vs pre-GIK states) showed that during GIK, angina occurred in only 4 patients, while significantly less severe changes were observed in ST depression (1.4±0.5 vs 2.4±0.4 mm) and LVEDPi (16±3 vs 23±3

mmHg). Lactate extraction was also higher (8.1±10.9 vs -5.2±11.1%), but not significantly so, although L became normal in 4 subjects and improved in another. These results indicate that GIK infusion was well tolerated and had a beneficial effect on pacing-induced myocardial ischemia.

The mechanism responsible for the beneficial effects of GIK on the pacing-induced ischemic syndrome remains speculative. Increased myocardial glucose uptake in the presence of insulin may have resulted in greater energy supply via enhanced anaerobic glycolysis or improved oxidative metabolism, although some of the glucose may have been directed also toward the synthesis of glycogen in the nonischemic myocardium. Furthermore, since data on coronary blood flow was not available in this study, the possibility that improved oxidative metabolism secondary to either increased total flow or redistribution of flow to the ischemic area cannot be clarified. These issues require further investigation.

99. Blood flow and release of free fatty acids in the omentum, mesentery and subcutaneous adipose tissue of the dog in haemorrhagic shock. A. G. B. Kovach, S. Rosell, P. Sándor, J. Hamar, K. Ikrényi, and E. Kovách. Acta Phys. Acad. Scient. Hung. 45: 79-87, 1974.

Blood flow, release of free fatty acids (FFA) and glycerol were measured in the subcutaneous, mesenteric and omental adipose tissues in chloralose-anaesthetized dogs during a standardized haemorrhagic shock procedure. Resting blood flows were 6.3±1.4 ml/min/100 g (±SEM) in the subcutis, 14.8±3.3 ml/min/100 g in the mesentery, and 5.3±1.2 ml/min/100 g in the omentum. There was a pronounced reduction of blood flow during bleeding to an arterial pressure of 55 mmHg for 90 min and it remained low during bleeding to 35 mmHg for an additional 90-min period. Blood flow in the mesentery was significantly higher than in the other two adipose tissues in both the control and the bleeding periods. There was no increase of FFA release from adipose tissue but glycerol release from the mesentery was significantly increased. The arterial concentration of FFA did not change but there was a significant elevation of the glycerol concentration from 0.21±0.04 mM to 0.95±0.22 mM ($p<0.05$). Arterial pH decreased from 7.28±0.03 to 7.06±0.04, and the lactate level rose from 3.18±0.38 to 10.66±1.61 mM during bleeding.

It is concluded that the low blood flow in adipose tissue following bleeding may impair the outflow of FFA and glycerol. Regional differences in the intensity of the blood flow reduction may be the explanation for the significant rise in the outflow of glycerol from the mesentery but not from the subcutis or the omentum. The reesterification of FFA increased following bleeding, presumably due to the high lactate concentration. As a consequence of the low pH, the lipolytic rate diminished in adipose tissue in spite of a presumably high sympathetic neurohumoral activity. The rise in the reesterification rate and inhibition of lipolysis as well as the diminution in adipose tissue blood flow counteracts the outflow of FFA.

100. Phagocytosis and erythroblastosis. I. Modification of the neonatal response by promethazine hydrochloride. J. P. Gusdon, Jr., M. R. Caudle, G. A. Herbst, and N. P. Iannuzzi. Am. J. Obstet. Gynec. 125: 224-226, 1976.

Phagocytic cells were obtained from children at ages comparable to those at which the disease is most commonly seen during pregnancy. The effect of P-HCl on the phagocytic action of these cells on opsonized red blood cells was studied in vitro.

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